**Supplementary Methods 1**

*Image Processing for Cortical Thickness Measurement*

With a linear transformation, native MRI images were registered into a standardized stereotaxic space (Collins *et al.*, 1994). The N3 algorithm was used to correct the images for intensity-based non-uniformities (Sled *et al.*, 1998) caused by the nonhomogeneities in the magnetic field. Then, the registered and corrected images were classified into white matter, gray matter, CSF, and background, using a 3D stereotaxic brain mask and the Intensity-Normalized Stereotaxic Environment for Classification of Tissues (INSECT) algorithm [Zijdenbos A]. The surfaces of the inner and outer cortex were automatically extracted using the Constrained Laplacian-Based Automated Segmentation with Proximities (CLASP) algorithm (Kim *et al.*, 2005).

Cortical thickness values were calculated in the native space rather than Talairach space because of the limitations in linear stereotaxic normalization. As we transformed MR volumes in native space into stereotaxic space with a linear transformation matrix, the inverse transformation matrix was applied to the cortical thickness models to reconstruct them in native space (Im *et al.*, 2006). Cortical thickness was defined as the Euclidean distance between the linked vertices of the inner and outer surfaces (Kim *et al.*, 2005). The thickness value was spatially normalized using surface-based two-dimensional registration with a sphere-to-sphere warping algorithm. Thus, the vertices of each subject were nonlinearly registered to a standard surface template (Lyttelton *et al.*, 2007; Robbins *et al.*, 2004). Cortical thickness was subsequently smoothed using a surface-based diffusion kernel in order to increase the signal-to-noise ratio. We chose 20 mm full-width at half-maximum as the kernel size to maximize statistical power while minimizing false positives (Chung *et al.*, 2003). For global and lobar regional analysis, the data of 30 normal subjects that had previously been manually categorized to lobes with high inter-rater reliability (Romero-Corral *et al.*, 2006) were registered to the template. The template then took the label of maximum probability in each vertex.

**References**

**Chung, M. K.*, et al.*** (2003). Deformation-based surface morphometry applied to gray matter deformation. *Neuroimage*, 18, 198-213.

**Collins, D. L., Neelin, P., Peters, T. M. and Evans, A. C.** (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Journal of Computer Assisted Tomography*, 18, 192-205.

**Im, K.*, et al.*** (2006). Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. *Neuroimage*, 31, 31-38. doi:10.1016/j.neuroimage.2005.11.042.

**Kim, J. S.*, et al.*** (2005). Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. *Neuroimage*, 27, 210-221. doi:10.1016/j.neuroimage.2005.03.036.

**Lyttelton, O., Boucher, M., Robbins, S. and Evans, A.** (2007). An unbiased iterative group registration template for cortical surface analysis. *Neuroimage*, 34, 1535-1544. doi:10.1016/j.neuroimage.2006.10.041.

**Robbins, S., Evans, A. C., Collins, D. L. and Whitesides, S.** (2004). Tuning and comparing spatial normalization methods. *Medical Image Analysis* 8, 311-323. doi:10.1016/j.media.2004.06.009.

**Romero-Corral, A.*, et al.*** (2006). Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*, 368, 666-678. doi:10.1016/s0140-6736(06)69251-9.

**Sled, J. G., Zijdenbos, A. P. and Evans, A. C.** (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging*, 17, 87-97. doi:10.1109/42.668698.

**Supplementary Table 1.** Baseline neuropsychological test results between the HE-AD and LE-AD

|  |  |  |  |
| --- | --- | --- | --- |
| **Tests (possible maximum score)** | HE-ADN = 23 | LE-ADN = 13 | p-value |
| *MMSE* | 21.4±3.3 | 20.2±3.1 | 0.282 |
| *CDR* | 0.8±0.3 | 0.8±0.2 | 0.459 |
| *CDR-SOB* | 4.4±1.8 | 5.3±1.7 | 0.145 |
| *Attention* |  |  |  |
| Digit span: forward (9) | 5.2±1.2 | 5.1±1.2 | 0.809 |
| Digit span: backward (8) | 2.9±0.9 | 2.7±0.6 | 0.220 |
| *Language and related functions* |  |  |  |
| BNT (60) | 37.3±9.2 | 34.8±8.1 | 0.609 |
| Calculation | 10.5±2.6 | 6.9±4.1 | 0.006 |
| Ideomotor praxis | 3.6±1.9 | 3.8±1.2 | 0.902 |
| *Visuospatial function* |  |  |  |
| RCFT (36) | 27.6±10.9 | 22.4±12.3 | 0.071 |
| *Memory* |  |  |  |
| SVLT: sum of three free recall trials(12+12+12 = 36) | 11.7±4.4 | 12.4±3.0 | 0.987 |
| SVLT: 20 min delayed recall (12) | 0.4±0.9 | 0.4±0.8 | 0.775 |
| SVLT: recognition (24) | 4.0±2.6 | 3.4±2.5 | 0.370 |
| RCFT: immediate recall (36) | 3.1±3.0 | 2.4±2.1 | 0.679 |
| RCFT: 20 min delayed recall (36) | 2.0±3.0 | 1.8±2.5 | 0.767 |
| RCFT: recognition (24) | 4.4±2.2 | 2.8±1.9 | 0.009 |
| *Frontal/executive function* |  |  |  |
| COWAT: animals | 10.0±4.4 | 9.5±3.9 | 0.643 |
| COWAT: supermarket items | 11.1±4.7 | 8.7±3.9 | 0.214 |
| COWAT: phonemic fluency with 3 letters | 17.4±9.8 | 10.5±6.3 | 0.038 |
| Stroop test: word reading in 2 min (112) | 102.6±22.8 | 98.8±23.2 | 0.810 |
| Stroop test: color reading in 2 min (112)  | 44.4±30.3 | 41.2±34.2 | 0.499 |

Values are mean ±SD of the raw score.

Baseline neuropsychological test results were analyzed using Mann-Whitney U test.

Abbreviations: BNT = the Boston Naming Test; CDR = Clinical Dementia Rating; CDR-SOB = Clinical Dementia Rating sum-of-boxes; COWAT = Controlled Oral Word Association Test; MMSE = Mini-Mental State Examination; RCFT = Rey-Osterrieth Complex Figure Test; SVLT = Seoul Verbal Learning Test

**Supplementary Table 2.** Longitudinal declines of neuropsychological tests over five years between the HE-AD and LE-AD

|  |  |  |
| --- | --- | --- |
| Group \* TimeNeuropsycholotical tests | Estimate (SE) | p*-*value |
| *MMSE* | 0.658 (0.506) | 0.196 |
| *CDR-SOB* | -0.209 (0.295) | 0.480 |
| *Attention* |  |  |
| Digit span: forward | 0.164 (0.170) | 0.338 |
| Digit span: backward | 0.045 (0.111) | 0.688 |
| *Language and related functions* |  |  |
| BNT | -0.052 (1.08) | 0.961 |
| Calculation | 0.460 (0.343) | 0.183 |
| Ideomotor apraxia | -0.028 (0.135) | 0.837 |
| *Visuospatial function* |  |  |
| RCFT | 0.217 (1.014) | 0.832 |
| *Memory* |  |  |
| SVLT: immediate recall | 0.365 (0.514) | 0.481 |
| SVLT: delayed recall | 0.109 (0.098) | 0.272 |
| SVLT : recognition  | 0.587 (0.485) | 0.231 |
| RCFT : immediate recall | -0.031 (0.228) | 0.892 |
| RCFT :delayed recall | 0.072 (0.264) | 0.786 |
| RCFT : recognition  | 0.493 (0.494) | 0.321 |
| *Frontal/executive function* |  |  |
| COWAT: animals | -0.046 (0.422) | 0.913 |
| COWAT: supermarket | 0.461 (0.482) | 0.342 |
| COWAT: phonemic | 1.556 (0.790) | 0.059 |
| Stroop test: word reading | -1.617 (3.612) | 0.655 |
| Stroop test: color reading | 0.679 (2.177) | 0.757 |

The group-by-time interaction effect in the neuropsychological results was analyzed using a linear mixed models with fixed effect factors of age, gender, and duration of disease, and a covariance pattern for repeated time points of Ar (1) correlation structure.

Abbreviations: BNT = the Boston Naming Test; CDR-SOB = Clinical Dementia Rating sum-of-boxes; COWAT = Controlled Oral Word Association Test; MMSE = Mini-Mental State Examination; RCFT = Rey-Osterrieth Complex Figure Test; SVLT = Seoul Verbal Learning Test

**Supplementary figure legends**

**Supplementary Fig. 1.** Statistical maps comparing differences in cortical thickness between the AD patients and NC. A) A statistical map of baseline difference in regional cortical thickness (FDR corrected Q value < 0.05). Regional difference at baseline was analyzed by general linear model with adjusting for age, gender, duration of disease, and intracranial volume. B) A statistical map of longitudinal decrease (group-by-time interaction) in cortical thickness from baseline to Year 5 (FDR corrected Q value < 0.05). The group-by-time interaction was analyzed by linear mixed models after controlling for age, gender, duration of disease, and intracranial volume.

Abbreviations: AD = Alzheimer’s disease; FDR= false discovery rate; NC = normal controls

**Supplementary Fig. 2.** Statistical maps of longitudinal decrease (group-by-time interaction) in cortical thickness from baseline to Year 5 in the AD patients. The group-by-time interaction was analyzed by linear mixed models after controlling for age, gender, duration of disease, intracranial volume, and using educational years as: A) continuous variable, B) HE-AD cut-off value > eight years, and C) HE-AD cut-off value > 10 years.

Abbreviations: AD = Alzheimer’s disease; HE = high education; LE = low education; NC = normal controls

**Supplementary Fig. 3.** Statistical maps in pairwise comparison of the HE-AD and LE-AD at each time point: A) Baseline – Year 1, B) Year 1 – Year 3, and C) Year 3 – Year5.

Significant findings were observed at Year 3 – Year 5 in terms of change in cortical thickness between the HE-AD and LE-AD in the bilateral parahippocampal and precuneus, the left temporo-parietal association, and the right prefrontal regions (FDR corrected Q value < 0.05).

Abbreviations: AD = Alzheimer’s disease; FDR= false discovery rate; HE = high education; LE = low education