Bridging the gap between Morphometric Similarity Mapping and gene transcription in Alzheimer's disease

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Abstract

Disruptions of brain connectivity have been widely reported in Alzheimer’s disease (AD). Morphometric similarity (MS) mapping provides a new way of estimating structural connectivity by inter-regional correlation of T1WI and DTI derived parameters within individual brains. Here, we aimed to identify AD-related MS changing patterns and genes related to the changes and further explore the molecular and cellular mechanism underlying MS changes in AD. Both 3D-T1WI and DTI data of 106 AD patients and well-matched 106 healthy elders from the ADNI database were included in our study. Cortical regions with significantly decreased MS were found in the temporal and parietal cortex, increased MS in the frontal cortex and variant changes in the occipital cortex in AD patients. Mean MS in regions with significantly changed MS was positively or negatively associated with memory function. The negative MS-related genes were significantly down-regulated in AD, specifically enriched in neurons, and participated in biological process with the most significant term in synaptic transmission. This study revealed AD-related cortical MS changes associated with memory function. Linking gene expression to cortical MS changes may provide a possible molecular and cellular substrate for MS abnormality and cognition decline in AD.

1. Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease marked by progressive neuron loss, manifested by short-term memory and other cognitive impairment symptoms(Wang et al. 2020). AD-related neurodegeneration involves several brain regions, in which the entorhinal, hippocampus and temporal cortices are the most reported(Femminella et al. 2018; Im et al. 2008; Lerch et al. 2005; Li et al. 2014; Morra et al. 2008; Seong et al. 2010). Structural indicators of these regions, including gray matter density(Frisoni et al. 2002), volume(Busatto et al. 2003), cortical thickness (Pettigrew et al. 2017), and curvature(Im et al. 2008; Seong et al. 2010) have been found decreased in AD patients. White matter studies based on diffusion tensor imaging (DTI) has also demonstrated reduced integrity in the temporal lobe, as well as white matter tracts connecting frontal and temporal regions in AD(Kantarci et al. 2017; Naggara et al. 2006). In recent years, AD has been widely regarded as a disconnected syndrome whereby a large-scale brain network is progressively disrupted by neuropathological processes. MR topological studies constructed whole-brain structural networks demonstrated abnormal topological properties in multiple brain regions including the hippocampus, frontal, temporal, parietal, and occipital regions, verifying the brain network disruption and disconnection between anatomically connected brain regions in AD patients(Lo et al. 2010; Yao et al. 2010).

All the above-mentioned structural findings are based on either gray matter (from 3D T1WI) or white matter (from DTI) parameters. Here we adopted a different parameter from the past — the "morphometric similarity (MS)" — which is estimated as the inter-regional correlation of multiple macro- and micro-structural multimodal MRI variables, based on both structural T1WI and DTI(Stam et al. 2007). It reflects the anatomical connections of different brain areas from histological similarity and axonal connectivity within an individual human brain(Seidlitz et al. 2018). Given that AD has been considered a disconnection syndrome (1) due to regional vulnerability to cellular neurodegeneration and disconnection of distant
cortical regions (Gonzalez-Escamilla et al. 2020), it is suitable to evaluate the brain anatomical connectivity in AD patients by using the MS as a neuroimaging indicator.

The Allen Human Brain Atlas (AHBA) can present gene transcription information in the same standard space as the neuroimaging data, providing a new approach for linking gene expression to neuroimaging phenotypes. With this approach, only a few reports combine gene transcription data with gray matter volumes in AD. However, it is unclear genes related to AD-specific MS changes are specific to which neurological functions and how the expression of these genes affects MS changes. In the current study, we investigated the MS changing pattern map in AD, and spatially associated the MS changing pattern map with the anatomically patterned gene expression using data from the AHBA. We aimed to identify AD-related MS changing patterns and genes closely related to the changes and further explore the cellular and molecular mechanism underlying MS changes in AD.

2. Material And Methods

2.1 Participates

When the study was initiated in September 2020, both 3D T1WI and DTI of 113 AD patients acquired at baseline were obtained from the ADNI database (http://adni.loni.ucla.edu), which followed the standard ADNI-GO and ADNI-2 protocol (Jack et al. 2010; Weiner et al. 2017). All images were visually checked by two radiologists, and seven patients with poor image quality (2 patients’ 3D T1WI and five patients’ DTI) were excluded. Finally, 106 AD patients with qualified image data were included (63 males and 43 females; mean age 75, ranging from 55 to 90 years). For comparison, the equal number of age and gender-matched healthy elders with qualified 3D-T1WI and DTI were selected from the ADNI database (63 males and 43 females; mean age 75, ranging from 55 to 90 years). The detailed scan parameters were provided in the Supplemental Table S1. The general cognitive function was assessed by the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating. The memory function was evaluated by a memory composite score obtained for the majority of participants (94 subjects with AD and 99 subjects with healthy elders) (Crane et al. 2012).

2.2 MS Estimation

The surface-based morphology parameter estimation from the high-resolution T1WI was performed using FreeSurfer v6.0.0 (http://surfer.nmr.mgh.harvard.edu/). The DTI data were preprocessed according to the pipeline of FMRIB’s Diffusion Toolbox implemented in FSL 5.0.10 (http://www.fmrib.ox.ac.uk). The detailed preprocessed procedures for T1WI and DTI data were provided in Supplement Material.

The DTI parameters of fractional anisotropy and mean diffusion were defined as myelination metrics. Among the surface-based morphology parameters, the gray matter, surface area and cortical thickness were defined as gray matter metrics, and the intrinsic/Gaussian curvature and mean curvature was curvature metrics.
To adjust variation from multiple sites and scanners, the ComBat harmonization of surface-based morphology and diffusion parameters across scanners and sites was performed before the downstream morphometric similarity estimation (Fortin et al. 2018; Fortin et al. 2017). Then, these metrics were Z-score transformed to improve normality.

The Pearson correlation of gray matter, curvature and myelination metrics between each pair of cortical regions was performed to generate 308 × 308 MS matrixes for each subject. Then, the 308 × 308 MS matrixes were averaged across the 308 cortical regions to calculate the regional MS for every 308 cortical regions. From the brain connectome perspective, the regional MS represents weighted degree of each cortical node, which was connected by signed and weighted edges of pairwise similarity to all other cortical nodes in the whole brain.

### 2.3 Transcription-Imaging Association

A compiled transcription matrix of six post mortem adult brains from the AHBA (http://human.brain-map.org/) was acquired from the data directory for Neuroscience in Psychiatry Network manuscript (https://doi.org/10.6084/m9.figshare.2057796.v1), which provided expression values for each of 20,737 genes estimated in 151 cortical regions of the left hemisphere. The PLS regression was used to identify genes whose transcriptional profiles were significant associated with regional MS difference. In this study, the independent variables were the compiled AHBA transcription matrix (151 regions × 20737 genes), and the dependent variables were the vector of regional MS case-control T values from the left hemisphere (151 regions). The first PLS component (PLS1) weight of each gene was assigned in terms of its contribution to the overall model. Then, the ratio of each gene's PLS1 weight to its bootstrapped standard error (1000 resampling with replacement of the 151 cortical regions) was calculated as a Z score. Here, genes with \(|Z\text{ score}| > 4.72\) (Bonferroni correction of \(P < 0.05\)) denote the PLS1 gene set. Details about the transcription-imaging association were provided in Supplement Material.

### 2.4 Disease Enrichment Analyses

Disease enrichment analyses was used to explore whether the PLS1 gene set enriched in AD-related differentially expressed genes (DEGs). The expression dataset with series accession number GSE5281 from the Gene Expression Omnibus database (http://www.ncbi.nlm.gov/geo) was acquired to screen the AD-related DEGs. The LIMMA package (version 3.42.2) of R software was used to analyze the DEGs between AD and normal elders. The \(P < 0.01\) and \(|\log_2(\text{fold change})| > 1\) were defined as the thresholds for screening AD-related DESs. Fisher's exact test was used to evaluate the significance of the overlap between PLS1 gene sets and AD-related DEGs. The Bonferroni method was used to correct for multiple comparisons (both up and down-regulated DEGs) \((P_c < 0.05, \text{ an uncorrected } P < 0.05/2 = 0.025)\). Details about the disease enrichment analyses were provided in Supplement Material.

### 2.5 Cell-Type-Specific Analysis

The RNAseq dataset with series accession number GSE73721 from the Gene Expression Omnibus database was acquired to perform cell-type-specific analysis. The pSI v1.1
was used to determine the specific neocortical cell type for which the PLS1-genes were enriched. A pSI threshold of 0.05 was used to generate the cell-type-enriched gene lists for each type of cortical cells. Fisher's exact test was used to evaluate the significance of the overlap between PLS1 gene sets and cell-type-specific genes for each type of cortical cells. The Bonferroni method was used to correct for multiple comparisons (5 cell-types) ($P_c < 0.05$, an uncorrected $P < 0.05/5 = 0.01$). Details about the cell-type-specific analysis were provided in Supplement Material.

### 2.6 Gene Ontology Analysis

The clusterProfiler package (v3.14.3) of R software was used to perform the gene ontology (GO) analysis. Our study only focused on the biological process of GO term that the PLS1 gene sets were enriched in. The Bonferroni adjusted $P$-value $< 0.05$ was considered significant.

### 2.7 The Statistical Analysis

The statistical analyses for demographic and cognition data were performed using the Statistical Package for the Social Sciences (SPSS version 18.0). Comparisons between AD and healthy elders were performed using a two-sample $T$ test for continuous variables with a normal distribution, and a chi-squared test for categorical variables. To test whether the MS of brain regions with significant case-control difference were associated with memory function, partial correlation analysis was conducted with age, gender and years of education as nuisance covariates. The Pearson correlation analysis was used to test the association between the $Z$ scored expression values of PLS1 gene sets and the $T$ statistics of case-control difference in MS. The resulting $P$ values above were Bonferroni corrected for multiple comparisons. The case-control difference in regional MS were estimated by fitting linear models with age, sex and education as covariates, and the resulting $P$ values for each region was false discovery rate (FDR) corrected for multiple comparisons.

### 3. Results

#### 3.1 Demographics and Cognition

A total of 106 AD patients and the same number of age and gender-matched healthy elders with qualified image data were finally included in the present study. The demographic and cognition data of these subjects are shown in Table 1. Significant differences were found in terms of MMSE ($P = 0.0001$), Clinical Dementia Rating ($P = 0.0001$) and memory composite scores ($P = 0.0001$). No significant differences were observed in terms of age ($P = 0.98$), gender ($P = 1$) or years of education ($P = 0.06$).
Table 1
Demographics and cognition

|                | AD (n = 106) | NC (n = 106) | T/χ² | P value |
|----------------|--------------|--------------|------|---------|
| Age, years     | 74.94 ± 8.02 | 74.92 ± 7.84 | 0.026| 0.979   |
| Education, years| 15.59 ± 2.60| 16.27 ± 2.50 | -1.92| 0.06    |
| Gender, male/female | 63/43   | 63/43       | 0    | 1       |
| MMSE           | 22.92 ± 3.13| 28.57 ± 1.73 | -16.26| 0.0001  |
| CDR            | 0.81 ± 0.27 | 0.04 ± 0.13  | 26.13| 0.0001  |
| Memory composite score* | -0.85 ± 0.50 | 0.79 ± 0.54 | -22.01| 0.0001  |

Note: The data are shown as means (SD). The star indicates the composite memory score was available from 94 of the 106 AD and 99 of the 106 NC. AD, Alzheimer’s disease; CDR, Clinical Dementia Rating; MMSE, mini-mental state examination; NC, normal control subject.

3.2 MS Differences Between AD and Healthy Elders

The cortical map in Fig. 1 demonstrated the significant differences in regional MS at each cortical area between AD and healthy elders. The cortical regions with significant decreased MS were observed in the left middle temporal lobe, left fusiform gyrus, bilateral banks of superior temporal sulci, bilateral parahippocampal lobes, left entorhinal cortex, left superior parietal lobe, left supramarginal gyrus, and right lateral occipital lobe (Table 2). The cortical regions with significant increased MS were found in bilateral superior frontal lobes, right paracentral lobe, right frontal pole cortex, left lingual gyrus and right lateral occipital lobe (Table 2). The partial correlation analysis showed that the mean MS average across the ten regions with decreased MS was significantly positively associated with memory composite score \(r = 0.43, P = 0.0001\), and the mean MS average across the nine regions with increased MS was significantly negatively associated with memory composite score \(r = -0.35, P = 0.0001\) (Fig. 2).
| Cortical regions                      | Coordinates (MNI) | T value | P value | FDR       |
|--------------------------------------|-------------------|---------|---------|-----------|
|                                      | x     | y      | z       |           |
| L_middletemporal_part5                | -60.019 | -27.635 | -13.299 | -4.8294  | 2.66E-06 | 7.74E-04 |
| L_fusiform_part1                      | -30.238 | -46.494 | -17.452 | -4.2592  | 3.11E-05 | 3.196E-04|
| R_bankssts_part1                      | 53.969  | -39.123 | 1.4973  | -4.1341  | 5.18E-05 | 3.986E-03|
| L_superiorparietal_part8              | -23.65  | -73.056 | 29.861  | -3.5866  | 4.18E-04 | 0.021429 |
| L_parahippocampal_part1               | -25.991 | -25.187 | -25.332 | -3.5065  | 5.57E-04 | 0.021429 |
| R_lateraloccipital_part2              | 44.513  | -70.022 | -2.0359 | -3.4184  | 7.59E-04 | 0.024105 |
| L_entorhinal_part1                    | -24.011 | -5.8614 | -32.827 | -3.4094  | 7.83E-04 | 0.024105 |
| L_bankssts_part2                      | -53.141 | -49.843 | 8.2646  | -3.2373  | 0.001405 | 0.035229 |
| R_parahippocampal_part2               | 27.448  | -24.861 | -24.205 | -3.0702  | 0.002426 | 0.04151  |
| L_supramarginal_part7                 | -49.357 | -38.912 | 32.554  | -3.0206  | 0.00284  | 0.046042 |
| R_superiorfrontal_part7               | 9.6868  | 8.2947  | 60.026  | 4.6868   | 5.03E-06 | 7.74E-04 |
| R_superiorfrontal_part11              | 9.2005  | 24.389  | 53.686  | 4.0632   | 6.87E-05 | 4.232E-03|
| R_paracentral_part2                   | 5.3566  | -16.772 | 61.135  | 3.5071   | 5.56E-04 | 0.021429 |
| R_frontalpole_part1                   | 9.8338  | 62.819  | -10.737 | 3.285    | 0.0011976| 0.033534 |
| R_lateraloccipital_part1              | 18.646  | -99.162 | -7.394  | 3.2203   | 0.001487 | 0.035229 |
| L_lingual_part2                       | -6.5596 | -88.407 | -8.0452 | 3.1896   | 0.001646 | 0.036218 |
| L_superiorfrontal_part2               | -11.687 | -8.4248 | 64.785  | 3.1488   | 0.001882 | 0.038635 |
| R_superiorfrontal_part6               | 10.21   | 54.909  | 26.16   | 3.1191   | 0.002073 | 0.039895 |
| R_superiorfrontal_part3               | 12.367  | -3.2651 | 65.643  | 3.0906   | 0.002272 | 0.041168 |

Note: The cortical regions above middle line of the table are regions with significant decreased morphometric similarity in AD, while cortical regions under middle line of the table are regions with significant increased morphometric similarity in AD. FDR, the corrected P value with false discovery rate method.

### 3.3 Gene-MS spatial correlations and characters

#### 3.3.1 PLS1 Gene Expression Associated with MS Difference
The PLS regression analysis revealed 1,932 genes with normalized PLS1 weights \( Z \) score < -4.72 (Bonferroni correction of \( P < 0.05 \)), which were defined as the PLS1- genes, and 2,139 genes with normalized PLS1 weights \( Z \) score > 4.72 (Bonferroni correction of \( P < 0.05 \)), which were defined as the PLS1+ genes (Supplemental Table S2). The majority of cortical regions on the PLS1+ gene expression map were in accordance with those on the case-control \( T \) map of regional MS (Fig. 3A, B), while the majority of cortical regions on the PLS1- gene expression map were in contrast with those on the case-control \( T \) map of regional MS (Fig. 3A, C). The Pearson correlation analysis revealed that the expression of PLS1+ genes was significantly positive correlated with regional MS difference (\( r = 0.45, P = 0.0001 \)) (Fig. 3D), while the expression of PLS1- genes was significantly negative correlated with regional MS difference (\( r = -0.44, P = 0.0001 \)) (Fig. 3E).

### 3.3.2 AD-Related DEGs Enrichment for PLS1- Genes

A total of 1,800 significant DEGs between AD and normal elders were identified from the GSE5281 series with 708 up-regulated and 1,092 down-regulated genes (Fig. 4A, Supplemental Table S3). Both up-regulated and down-regulated genes were defined as the AD-related DEGs. The enrichment analysis revealed that PLS1- genes were significantly enriched in down-regulated DEGs (\( Pc = 5.43 \times 10^{-12} \)), while not in up-regulated DEGs (\( Pc = 1 \)) (Fig. 4B, D). In addition, PLS1+ genes were neither significantly enriched in up-regulated DEGs (\( Pc = 1 \)) nor in down-regulated DEGs (\( Pc = 1 \)) (Fig. 4C, E).

### 3.3.3 Cell-Type Specificity of PLS1- Genes

The cell-type-enriched gene lists for each type of cortical cells are provided in the Supplemental Table S4. The PLS1- genes showed significant specific expression in neurons (\( Pc = 1.83 \times 10^{-5} \)) and astrocytes (\( Pc = 1.74 \times 10^{-5} \)), while not in oligodendrocytes (\( Pc = 1 \)) and microglia (\( Pc = 0.57 \)) (Table 3, Fig. 5A). The PLS1+ genes were not significantly enriched in any type of neocortical cells (\( Pc = 1 \) for all) (Table 4, Fig. 5B).

|                | Astrocytes | Neurons | Oligodendrocytes | Microglia |
|----------------|------------|---------|------------------|-----------|
| Overlapped genes | 139        | 195     | 33               | 71        |
| Cell-type-specific genes | 1160      | 1770    | 684              | 746       |
| Gene ratio | 0.12       | 0.11    | 0.048            | 0.095     |
| \( Pc \) values | \( 1.83 \times 10^{-5} \) | \( 1.74 \times 10^{-5} \) | 1        | 0.57      |

Table 3

The significance of the overlap between PLS1- genes and cell-type-specific genes

Note: PLS1, the first component of partial least squares regression; Overlapped genes, the number of overlapped genes between PLS1- genes and cell-type-specific genes; Gene ratio, gene ratio between the number of overlapped genes and the number of cell-type-specific genes; \( Pc \) values, the Bonferroni corrected \( P \) values.
3.3.4 GO Enrichment for PLS1- Gene Sets

The GO analysis revealed that significant biological processes of the PLS1- genes were mainly enriched in the neuron-specific terms, including synaptic signaling, neurotransmitter release, axonogenesis, and cognition (Fig. 6A, Supplemental Table S5). However, the PLS1 + genes were involved in the non-neuron-specific biological process, including potassium ion transport and protein localization (Fig. 6B, Supplemental Table S5).

4. Discussion

4.1 MS changing patterns and associated memory function in AD

This study showed that AD patients had decreased regional MS in multiple AD-susceptible regions among the temporal and parietal cortex. Additionally, increased regional MS in several frontal areas and variable changing MS in parts of the occipital cortex were also detected in AD patients compared with healthy elders. The mean MS average across those regions with decreased regional MS was positively associated with memory function. In contrast, the mean MS average across those regions with increased regional MS was negatively associated with memory function.

Our findings were consistent with a large number of studies reporting decreased gray matter volume and cortical thickness (Femminella et al. 2018; Lerch et al. 2005), the lower average mean curvature (Im et al. 2008; Morra et al. 2008), and shallower sulcal depth (Im et al. 2008) in the hippocampus, temporal lobe, fusiform gyrus and entorhinal cortex in AD, with the left hemisphere being dominant. DTI studies revealed disruptions of white matter integrity in the early stage of AD in limbic fiber tracks with direct connections to medial temporal lobe structures (Kalus et al. 2006; Sexton et al. 2010; Zhang et al. 2007). Moreover, decreased connectivity of multiple brain regions, including the temporal lobe, hippocampus, fusiform gyrus, and parietal lobe, has also been documented as the cause of the cognitive decline in AD.
patients (Bokde et al. 2006; He et al. 2008; Stam et al. 2007). Decreased MS in multiple brain regions, including the temporal, parietal, and part of occipital cortical regions in AD, reflected the weakening of the above-mentioned brain regions’ anatomical connections from the histological and cellular architecture level and implied increased architectonic differentiation and decreased axonal connectivity between these cortical regions. We further found a correlation between the weakening of this anatomical connection and the impairment of memory function, suggesting that the anatomical disconnection caused by the reduction of the similarity of histology and cellular architecture may be the neural basis for the impairment of memory function in AD patients.

Our result of elevated MS in the prefrontal areas in AD patients suggested increased architectonic similarity and enhanced axonal connectivity in the prefrontal regions in AD patients, which consistent with enhanced functional activation and connectivity within frontal regions in early stage of AD (Aganj et al. 2020; Grady et al. 2003). We tend to interpret the increased prefrontal MS in AD as a compensatory reallocation of cognitive resources. This explanation was further supported by the negative correlation between the average MS value of the brain areas with increased MS and memory function in AD patients. The more compensatory increase of MS, the worse the performance of memory function. As the disease becomes severe, the compensatory increase may disappear, but this needs to be confirmed by future longitudinal studies. The inconsistent MS changes patterns in the occipital areas in AD patients may be related to different functional areas with different changing patterns in the occipital lobe, which was supported by the evidence of the dissociation between impaired explicit memory encoding in secondary visual areas and intact implicit encoding in primary visual cortex in AD.

4.2 Linking gene expression to MS Difference map and functional annotation

PLS analysis showed that the PLS1 + gene was positively correlated with the AD-related MS difference map, and PLS1-gene was negatively correlated with the AD-related MS difference map. However, only PLS1- genes were significantly enriched in down-regulated AD-related DEGs. GO analysis and Cell-type-specific analysis showed that the PLS- genes were cytologically enriched in neurons and astrocytes, and functionally involved in the neuron-specific biological process, including synaptic signaling, neurotransmitter release, axonogenesis, and cognition. Because PLS1 + genes were not enriched in AD differential genes, and implicated in non-neuron-specific functions, the following discussion mainly focuses on the PLS1- genes.

The PLS1- genes showed significant specific expression in neurons and astrocytes. Neurons begin to die early in AD pathogenesis. Exposure of astrocytes to Aβ may induce astrocyte activation (Diniz et al. 2017) and release pro-inflammatory cytokines, contributing to neuron death (Wood et al. 2015). In our study, a series of AD protective genes related to nerves and astrocytes were significantly downregulated, leading to neural axon deterioration, causing histological similarity and anatomical connectivity destruction, and thus MS reduction (Lane et al. 2018; Verkhratsky et al. 2010).
In our study, PLS1- genes were enriched in biological processes of synaptic signaling, neurotransmitter release, axonogenesis, and cognition. The loss of neurons and synapses and axon destruction are common findings in AD neuropathology and are related to cognition decline in AD patients. The hippocampus, temporal, and parietal cortex were areas where synapses more vulnerable to loss. By contrast, synapses in the frontal cortex were resistant to AD's pathological process even in the late stage of the disease (Minger et al. 2001). The different changing patterns of AD-related synaptic proteins are highly consistent with the changing patterns of AD-related local MS shown in our results.

In summary, this study revealed AD-related cortical MS changes associated with memory function. Linking gene expression to cortical MS changes, the negative MS-related genes were found enriched explicitly in neurons and astrocytes, participated in the neuron-specific biological process, and were significantly down-regulated in AD. These findings may provide a possible molecular and cellular substrate for MS abnormality and cognition decline in AD.

Declarations

Author contributions

Junlin Shen and Yang Zhang conceived of the idea. Min Ma and Zhonghua Xie analyzed the MRI data. Heng Wu analyzed the transcription data. Nan Zhang analyzed the behavioral data. Yang Zhang wrote the initial draft. All authors agreed with the final version of the manuscript.

Disclosures of Conflicts of Interest

The authors declare no conflict of interest

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Tables

**Table 1** Demographics and cognition

|                  | AD (n=106)    | NC (n=106)    | t/χ²  | P value |
|------------------|---------------|---------------|-------|---------|
| Age, years       | 74.94±8.02    | 74.92±7.84    | 0.026 | 0.979   |
| Education, years | 15.59±2.60    | 16.27±2.50    | -1.92 | 0.06    |
| Gender, male/female | 63/43       | 63/43       | 0     | 1       |
| MMSE             | 22.92±3.13    | 28.57±1.73    | -16.26| 0.0001  |
| CDR              | 0.81±0.27     | 0.04±0.13     | 26.13 | 0.0001  |
| Memory composite score* | -0.85±0.50  | 0.79±0.54     | -22.01| 0.0001  |

Note: The data are shown as means (SD). The star indicates the composite memory score was available from 94 of the 106 AD and 99 of the 106 NC. AD, Alzheimer’s disease; CDR, Clinical Dementia Rating; MMSE, mini-mental state examination; NC, normal control subject.
Table 2: Cortical regions of case-control differences in regional morphometric similarity

| Cortical regions                  | Coordinates (MNI) | Tvalue | Pvalue      | FDR       |
|----------------------------------|-------------------|--------|-------------|-----------|
| L_middletemporal_part5           | -60.019 -27.635 -13.299 | -4.8294 | 2.66E-06    | 7.74E-04  |
| L_fusiform_part1                 | -30.238 -46.494 -17.452 | -4.2592 | 3.11E-05    | 3.196E-04 |
| R_bankssts_part1                 | 53.969 -39.123 1.4973   | -4.1341 | 5.18E-05    | 3.986E-03 |
| L_superiorparietal_part8         | -23.65 -73.056 29.861   | -3.5866 | 4.18E-04    | 0.021429  |
| L_parahippocampal_part1          | -25.991 -25.187 -25.332 | -3.5065 | 5.57E-04    | 0.021429  |
| R_lateraloccipital_part2         | 44.513 -70.022 -2.0359  | -3.4184 | 7.59E-04    | 0.024105  |
| L_entorhinal_part1               | -24.011 -5.8614 -32.827 | -3.4094 | 7.83E-04    | 0.024105  |
| L_bankssts_part2                 | -53.141 -49.843 8.2646   | -3.2373 | 0.001405    | 0.035229  |
| R_parahippocampal_part2          | 27.448 -24.861 -24.205  | -3.0702 | 0.002426    | 0.04151   |
| L_supramarginal_part7            | -49.357 -38.912 32.554   | -3.0206 | 0.00284     | 0.046042  |
| R_superiorfrontal_part7          | 9.6868 8.2947 60.026    | 4.6868  | 5.03E-06    | 7.74E-04  |
| R_superiorfrontal_part11         | 9.2005 24.389 53.686    | 4.0632  | 6.87E-05    | 4.232E-03 |
| R_paracentral_part2              | 5.3566 -16.772 61.135   | 3.5071  | 5.56E-04    | 0.021429  |
| R_frontalpole_part1              | 9.8338 62.819 -10.737   | 3.285   | 0.0011976   | 0.033534  |
| R_lateraloccipital_part1         | 18.646 -99.162 -7.394   | 3.2203  | 0.001487    | 0.035229  |
| L_lingual_part2                  | -6.5596 -88.407 -8.0452  | 3.1896  | 0.001646    | 0.036218  |
| L_superiorfrontal_part2          | -11.687 -8.4248 64.785   | 3.1488  | 0.001882    | 0.038635  |
| R_superiorfrontal_part6          | 10.21 54.909 26.16     | 3.1191  | 0.002073    | 0.039895  |
| R_superiorfrontal_part3          | 12.367 -3.2651 65.643    | 3.0906  | 0.002272    | 0.041168  |

Note: The cortical regions above middle line of the table are regions with significant decreased morphometric similarity in AD, while cortical regions under middle line of the table are regions with significant increased morphometric similarity in AD. FDR, the corrected P value with false discovery rate method.

Table 3: The significance of the overlap between PLS1- genes and cell-type-specific genes

|                     | Astrocytes | Neurons | Oligodendrocytes | Microglia |
|---------------------|------------|---------|-----------------|-----------|
| Overlapped genes    | 139        | 195     | 33              | 71        |
| Cell-type-specific genes | 1160       | 1770    | 684             | 746       |
| Gene ratio          | 0.12       | 0.11    | 0.048           | 0.095     |
| Pc values           | 1.83×10⁻⁵  | 1.74×10⁻⁵ | 1              | 0.57      |

Note: PLS1, the first component of partial least squares regression; Overlapped genes, the number of overlapped genes between PLS1- genes and cell-type-specific genes; Gene ratio, gene ratio between the number of overlapped genes and the number of cell-type-specific genes; Pc values, the Bonferroni corrected P values.
Table 4 The significance of the overlap between PLS1+ genes and cell-type-specific genes

|                    | Astrocytes | Neurons  | Oligodendrocytes | Microglia |
|--------------------|------------|----------|------------------|-----------|
| Overlapped genes   | 67         | 153      | 62               | 61        |
| Cell-type-specific genes | 1160     | 1770     | 684              | 746       |
| Gene ratio         | 0.058      | 0.086    | 0.091            | 0.082     |
| Pc values          | 1          | 1        | 1                | 1         |

Note: PLS1, the first component of partial least squares regression; Overlapped genes, the number of overlapped genes between PLS1+ genes and cell-type-specific genes; Gene ratio, ratio between the number of overlapped genes and the number of cell-type-specific genes; Pc values, the Bonferroni corrected P values.

Figures
Figure 1

Case-control differences in regional morphometric similarity (P < 0.05, FDR corrected). Regions in blue color indicate significant decreased morphometric similarity in AD, while regions in red color indicate significant increased morphometric similarity in AD. FDR, false discovery rate; L, left; R, right.
Figure 2

The relationship between memory composite score and the regional morphometric similarity. (a) The averaged morphometric similarity in regions with significant increased morphometric similarity in AD is significantly negative with memory composite score. (b) The averaged morphometric similarity in regions with significant decreased morphometric similarity in AD is significantly positive with the memory composite score.
Figure 3

The relationship between PLS1 gene sets expression and regional morphometric similarity difference. (a) The regional morphometric similarity case-control T map in the left hemisphere. The regions in red color indicate the increased morphometric similarity in AD, while the blue color indicated the decreased morphometric similarity in AD. (b) The PLS1+ gene set expression map illustrates that regions in red color are increased expression of PLS1+ gene set, while regions in blue color are decreased expression of PLS1+ gene set. (c) The PLS1- gene set expression map illustrates that regions in red color are increased expression of PLS1- gene set, while regions in blue color are decreased expression of PLS1- gene set. (d)The point plot in red shows that expression of PLS1+ gene set is significantly positive correlated with regional morphometric similarity difference between AD and healthy elders. (e) The blue point plot showed that expression of PLS1- gene set is significantly negative correlated with regional morphometric similarity difference between AD and healthy elders.
AD-related DEGs enrichment analyses for PLS1 gene sets. (a) The volcano plot shows 708 up-regulated genes in red color on the right and 1,092 down-regulated genes in blue color on the left. (b) The PLS1-genes are significantly overlapped with down-regulated genes. The number of overlapped genes is 176, accounting for 0.9% of total genes. The purple circle indicates 1092 down-regulated genes, the yellow circle indicates 1,932 PLS1- genes, and the green circle indicates the 20,177 background genes. (c) The

Figure 4

AD-related DEGs enrichment analyses for PLS1 gene sets. (a) The volcano plot shows 708 up-regulated genes in red color on the right and 1,092 down-regulated genes in blue color on the left. (b) The PLS1-genes are significantly overlapped with down-regulated genes. The number of overlapped genes is 176, accounting for 0.9% of total genes. The purple circle indicates 1092 down-regulated genes, the yellow circle indicates 1,932 PLS1- genes, and the green circle indicates the 20,177 background genes. (c) The
PLS1+ genes are not significantly overlapped with down-regulated genes. The number of overlapped gene is 126, accounting for 0.6% of total genes. The purple circle indicates 1,092 down-regulated genes, the yellow circle indicates 2,139 PLS1+ genes, and the green circle indicated 20,177 background genes. (d) The PLS1- genes are not significantly overlapped with up-regulated genes. The number of overlapped gene is 49, accounting for 0.2% of total genes. The purple circle indicates 708 up-regulated genes, the yellow circle indicates 1,932 PLS1- genes, and the green circle indicates 20,177 background genes. (e) The PLS1+ genes are not significantly overlapped with up-regulated genes. The number of overlapped gene is 66, accounting for 0.3% of total genes. The purple circle indicates 708 up-regulated genes, the yellow circle indicates 2,139 PLS1+ genes, and the green circle indicates 20,177 background genes. DEGs, differentially expressed genes; FC, fold change; PLS, partial least squares regression.

Figure 5

The percentage of gene ratio between overlapped genes and cell-type-specific genes for each type of neocortical cell. (a) The PLS1- genes significantly overlap with cell-type-specific genes in neurons and astrocytes (asterisk), while don not in oligodendrocytes and microglia. (b) The PLS1+ genes don not significantly overlap with cell-type-specific genes in any type of neocortical cell.
Figure 6

The significant Gene Ontology terms of biological process for PLS1 gene sets. (a) The PLS1- genes are significantly enriched in synaptic signaling, neurotransmitter release, axonogenesis and cognition. (b) The PLS1+ genes are significantly enriched in potassium ion transport and protein localization. Pc, the Bonferroni corrected P values.

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