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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	All statistical analyses and plotting were conducted in R 3.6.0 using the following packages: lmer4 (v1.1-26) for linear mixed-effects models; emmeans (v1.3.5) for extracting model estimates; ggplot2 (v3.3.3), tigris (0.9.4), and choroplethrZip (1.5.0) for plotting. Block-level matrix permutation was conducted in MATLAB 2019a using in-house scripts. Longitudinal spring-embedded graphs were generated using SoNIA (1.2.2), and exported through Cytoscape (3.2.0) to generate high resolution image. Visualization of nodes on the cortical surfaces were generated using Connectome Workbench (1.3.2). Functional MRI (fMRI) BOLD images (resting-state) were processed through an in-house fMRI preprocessing pipeline using Nipype 0.8.0, FSL 5.0.2.2. Structural images were processed through FreeSurfer 5.3. The calculation of brain network segregation uses custom code available on https://github.com/mychan24/system_matrix_tools. A modified version of superheat package was used to generate heatmaps in the supplemental material (https://github.com/mychan24/superheat).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Data includes patient information and are private and unsuitable for public deposition. Imaging and behavioral data are available to investigators upon request and approval from the Knight ADRC Leadership Committee. The ADRC Leadership Committee meets the second Monday of January, March, May, July, September, and November each year. Data requests are approved on a rolling basis. Requests involving neuroimaging data should be submitted to the ADRC for preliminary review prior to the Leadership Committee meeting (Director of Imaging Core – Dr. Tammie Benzinger, benzingert@wustl.edu). Detailed instructions for making a request can be found on https://knightadrc.wustl.edu/Research/ResourceRequest.htm

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Quantitative longitudinal study.
Research sample	The data was obtained from an existing dataset, collected at Washington University Knight Alzheimer's Disease Research Center (ADRC). The research questions necessitates a dataset with longitudinal resting-state data, neuropathology data, and clinical diagnosis of dementia. Furthermore, it was important that the participant sample exhibited heightened Alzheimer's Disease-related risk (e.g., higher proportion of APOE e4 participants), resulting in adequate statistical power to examine the research question. The data included adult participants that were tested two times or more to form a longitudinal sample. The final sample, after quality control check included 265 unique participants (154F; aged 45-86y at at baseline testing). The sample included middle-aged and older adults because this was the approximate age-range when the hypothesized brain changes would be observed.
Sampling strategy	This study uses an archival dataset. We conducted a power analysis prior to requesting the data based on previously published work reporting a SES by age interaction on brain system segregation with a partial eta squared of .03 (Chan et al. 2018). The statistical effect of interest (3-way interaction of a mixed-effects approach) required a minimum of 168 participants (achieving 95% power, alpha =0.05, effect size f=0.176 [converted from partial eta squared of 0.03]). The final sample size exceeded the minimum requirement.
Data collection	Participants complete repeated (longitudinal) clinical assessments at the Knight ADRC. The clinical assessment includes a full neurological examination and administration of the Clinical Dementia Rating (CDR) by trained clinicians. Only the CDR and corresponding sum of boxes score were used in the present study. Neuropathology: As previously described in Fagan et al. (2006, Ann Neurol), cerebral spinal fluid (CSF) was collected at 8am after overnight fasting. A trained neurologist collects the sample in a polypropylene tube via gravity drip using 22-gauge Sprotte spinal needle. CSF sample was gently inverted and briefly centrifuged at low speed to pellet any cellular elements; and then aliquoted (500 µl) into polypropylene tubes before freezing at -84°C until time of assay. CSF samples were measured using commercial enzyme-linked immunosorbent assay (Innotest; Innogenetics, Ghent, Belgium). As previously described in Mintun et al. (2006, Neurology), amyloid positron emission tomography (PET) images were collected using [11C] Pittsburgh Compound B (PiB) or Forbetapir (18FAV-45). Only PiB data were used in the present study. Standard uptake value ratios (SUVR) were calculated based on 30-60 minute post-injection window for PiB data. MRI: Participants were scanned using a Siemens 3T Trio or a Siemens Biograph mMR PET/MR scanner (Siemens, Malvern, PA) at the Center for Clinical Imaging Research located at the Washington University Medical Center. See magnetic resonance imaging section below for detailed sequence and processing information. Genetics: APOE genotyping was obtained from each participant's blood sample. APOE e4 positive status was coded based on the presence of at least one e4 allele. Researchers are present when data are being collected. The study has no experimental vs. control condition.
Timing	This study used a subset of data from the Knight ADRC data. Of the data that was obtained for this study, the earliest MRI scan date was 01/2007, and the latest scan date was 12/2016. The MRI data was collected on a rolling basis. Based on the earliest available MRI data, clinical data collected within a year of the baseline MRI data, from 05/2006 until 05/2019 were used.

Data exclusions	A total of 417 participants from the Knight ADRC with two or more resting-state scans were preprocessed with a resting-state fMRI preprocessing pipeline. 28 participants failed preprocessing QC (e.g., poor skull-stripping, poor segmentation from FreeSurfer), 116 participants did not pass the QC for having adequate data after head-motion correction ('scrubbing'), 7 participants failed surface-mapping QC. Lastly, a single participant with a baseline Clinical Dementia Rating scale (CDR) of 1 was excluded. This resulted in a total of 265 unique participants with 2 or more resting-state scans.
Non-participation	Data-collection is on-going. Participant status or attrition data was not available as part of the data request.
Randomization	No experimental/control group assignment was used in the current study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	See above
Recruitment	Participants in the present study include a subset of participants recruited in studies under the Knight ADRC. Participants in Knight ADRC are recruited from the metropolitan St. Louis, Missouri region. Recruitment methods include word of mouth, physician referrals, and community recruitment activity. The present dataset drew from a broader Knight ADRC dataset pool which is relatively diverse and representative of the catchment area where the data was collected. However, as is the problem with many neuroimaging studies, the final participant sample that passed rigorous data quality control included few participants with very low education (< high school) and also included fewer non-white participants than would be expected based on the broader Knight ADRC data sample. In addition to possible selection biases due to health or education, longitudinal measurement also exposes the data to attrition bias, where individuals with poorer health and by association, poorer cognition, are less likely to remain in the study. Altogether, the detrimental effect of lower education on the declining trajectory of brain system segregation and the latter's relation to clinical decline are likely under-estimated given the health disparities that are prevalent among lower educated adults. These limitations add constraints to interpretation of the observed relationships.
Ethics oversight	The Knight ADRC study has been approved by the Human Research Protections Office of Washington University in St. Louis. Informed consent was obtained from all participants in the study. The analysis of Knight ADRC data included in the present work was approved by the Institutional Review Board of The University of Texas at Dallas.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Magnetic resonance imaging

Experimental design

Design type	Resting-state
Design specifications	During each of these resting-state scans, participants were instructed to fixate on a visual cross-hair, remain still and keep their eyes open, and not fall asleep. In general, each imaging session included 2 runs of resting-state scans, each consisting of 164 volumes. However, there were 5 total sessions of data that included extra resting-state scans (four with 3 runs, and a single session had 4 runs); participant data for each of these sessions was inspected and processed along with the first two runs available for that session.
Behavioral performance measures	Resting-state fMRI is a task-free protocol and does not have behavioral performance measures.

Acquisition

Imaging type(s): resting-state fMRI, T1 MPRAGE

Field strength: 3

Sequence & imaging parameters: T1-weighted anatomical images were obtained using a magnetization-prepared rapid-acquisition gradient echo sequence (MPRAGE; repetition time [TR] = 2400ms, echo time [TE] = 3.16ms; flip angle = 8°; field of view [FOV] = 256 × 256mm; slices = 176; resolution = 1 × 1 × 1mm). Resting-state functional correlations were computed using functional brain images that are sensitive to blood oxygen level-dependent (BOLD) activity obtained using an echo-planar sequence (TR = 2200ms, TE = 27ms; flip angle = 90°; FOV = 256 × 256mm; slices = 36, interleaved acquisition; resolution = 4 × 4 × 4mm).

Area of acquisition: whole brain

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: T1 images were processed using FreeSurfer 5.3 to obtain the participant's cortical surface, cortical thickness measure, and hippocampal volume at each time point. Manual examination was performed on all FreeSurfer outputs, and when necessary, manual editing (i.e., control points, white/pial surface edits) was performed to ensure accurate construction of the cortical surface.

BOLD images (resting-state) were processed through an in-house fMRI preprocessing pipeline using Nipype 0.8.0: (i) slice-timing correction to remove odd-even slice intensity differences due to interleaved acquisition, (ii) rigid body correction for estimating and correcting head movement between volumes, and (iii) realignment to the a T1 weighted image from the same session. All steps were done using FSL 5.0.2.2 except for realignment between volumes and rigid body correction, where SPM8 was used as it provided more accurate estimates in our sample. Functional data in volume-space was not smoothed since the data were surface-mapped to the fs_LR surface template, and smoothed using a Gaussian smoothing kernel (σ=2.55) on the surface.

Normalization: Participants' anatomical image was used to construct their cortical surface. Anatomical image was deformed to the fsaverage surface using FreeSurfer, version 5.3. The left and right fsaverage surfaces were then registered to a hybrid left-right fsaverage atlas (fs_LR).

Functional data were registered to the fs_LR (32k) surface-based atlas for analysis. Using the transformation matrix and deformation maps generated during the preprocessing of the corresponding anatomical data, the volumetric functional data were resampled to the fs_LR surfaces through a one-step transformation.

Normalization template: The fs_LR atlas is a hybrid left–right fsaverage surface. The fsaverage-registered left and right hemisphere surfaces were brought into register with each other using deformation maps from a landmark-based registration of the left and right fsaverage surfaces (Van Essen et al. 2012).

Noise and artifact removal: Multiple regression to remove variance related to whole-brain signal, ventricular signal, white matter signal, their derivatives, and the "Friston24" motion regressors.

Volume censoring: In-house scripts written in MATLAB was used to censor volumes that exceed frame-wise displacement of 0.3mm, or were between two contaminated volumes that were less than 5 volumes apart. Participants with less than 100 volumes of data after censoring were excluded from further analysis.

Statistical modeling & inference

Model type and settings: N/A. Graph theory based technique was used to extract network summary index for each participant.

Effect(s) tested: Resting-state fMRI does not have a task or stimulus condition. Linear mixed effects models were used to analyze changes in network summary measure.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☒ Both

Anatomical location(s): Functionally defined resting-state ROIs across the entire cortex (349 3mm radius disks) were used to construct a network graph (Chan et al. 2014; 2017).

Statistic type for inference (See Eklund et al. 2016): Voxel wise and cluster-wise analyses were not performed. Linear mixed effects models were used to analyze changes in network summary measure. Permutation (10,000) was used to examine block level system changes.

Correction: FDR correction was applied to block level system change analysis.

Models & analysis

n/a	Involved in the study
☐	☒ Functional and/or effective connectivity
☐	☒ Graph analysis
☒	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity	Fisher's z-transformed Pearson's correlation
Graph analysis	A global summary measure, brain system segregation (Chan et al. 2014), was calculated using weighted graph on the subject-level.