nature portfolio

Corresponding author(s): James M Roe

Last updated by author(s): Sep 30, 2024

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

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 for the current study.
Data analysis	FreeSurfer v7.1; R version 4.0.0 ("gamm4" v 0.2.6; "xgboost" v 1.4.1.1), PLINK 1.90 All code underlying the statistical analyses is available at https://github.com/jamesmroe/ADchangeRisk and archived at https://doi.org/10.5281/zenodo.13861219

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The individual-level data supporting the results of the current study may be available upon request, given appropriate ethical and data protection approvals. Different limitations on data access apply to different samples. Participants in LCBC, BETULA and NESDA have not consented to share their data publicly online.

Requests for the raw data can be submitted to the relevant principal investigator of each contributing study. Contact details are provided in Supplementary Note 2. ADNI and AIBL data are available at https://adni.loni.usc.edu/data-samples/access-data/ pending application approval and compliance with the data usage agreement. Summary-level source data are provided with this paper (Source Data files).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was used as a covariate-of-no-interest in all statistical analyses. We did not perform any sex-specific or sex-stratified analyses as this was not a primary aim of this work. Information on sex but not gender was obtained at the time of data collection.
Reporting on race, ethnicity, or other socially relevant groupings	We did not use any socially constructed or socially relevant categorization variables in statistical analyses. Only individuals with genetic European ancestry were included in polygenic risk analyses, whereas the brain change estimation procedure made use of data from all individuals with longitudinal follow-up data, regardless of race or ethnicity. In addition, the top 10 genetic principal components were included as covariates to control for population structure.
Population characteristics	Demographic information on each of the study samples is available in Supplementary Tables 2 and 4 and described in the Methods.
Recruitment	This manuscript made use of pre-collected MRI datasets and the recruitment procedures for each contributing study have been thoroughly described previously (see references in Methods). For the in-house LCBC dataset, we provide a thorough description of each of the sub-studies that comprised the LCBC sample in Supplementary Note 1, including details on recruitment. No MRI sample is fully representative of the populations from which they are drawn. Which effects this may have on the results are unknown.
Ethics oversight	All procedures were approved by a relevant ethics review board. For Lifebrain, approval was given by the Regional Ethical Committee for South Norway, and all sub-studies were approved by the relevant national review boards.

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

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

Life sciences study design

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

Sample size	Adult lifespan datasets: MRI sample sizes were determined based on data availability. No analyses were performed to pre-determine sample sizes. We gathered as much longitudinal MRI data as we could from individuals aged 30 years and above. All MRI scans that did not fail FreeSurfer processing from each dataset were initially included. AD datasets: For AIBL data, we used all available MRI observations of non-reverting individuals who were diagnosed with Alzheimer's disease (AD) by their final timepoint, and all observations from individuals deemed to be cognitively healthy at every timepoint, following our previous work (https://doi.org/10.1038/s41467-021-21057-y). This also applied to the ADNI dataset, but with two exceptions. First, to ensure better accuracy of individual-specific brain change estimates in ADNI legacy data, we imposed the additional constraint that ADNI individuals should not change scanner field strength across timepoints, and kept only observations from the field strength with the most timepoints on a per-individual basis (or where equal, kept the 3T scans). Second, we included observations from reverting individuals in ADNI as long as their final diagnosis was AD. This latter consideration was taken due to the much larger sample size of ADNI (relative to AIBL), where including longitudinal scans from individuals reverting between diagnoses was deemed to pose minimal risk to the validity of the longitudinally defined AD group. Similarly, the a priori decision to not include reverting individuals in AIBL test data was taken to ensure the validity of the longitudinally defined AD group, following our previous work. Genetic observations: For polygenic score analyses, we used all available genetic observations passing quality control of individuals with European ancestry from the adult lifespan cohorts (LCBC, BETLUA, and NESDA). Memory observations: To estimate adult lifespan memory-change in the LCBC discovery sample, we used all available longitudinal observations on the California Verbal Learning Test, after discarding data originating from individuals in on-off memory training studies (see SI Note 1 for detailed information on the sub-studies that comprised the LCBC discovery sample.
Data exclusions	LCBC discovery sample: Exclusion criteria were pre-established to guard against the possibility of including participants with incipient AD in the sample: we excluded adults whose scores on the Mini Mental State Exam (MMSE) suggested longitudinal cognitive deficit with no later recovery (MMSE < 25 at their final timepoint; 2 participants; 4 scans), and adults aged 40+ whose scores on the Beck Depression Inventory (BDI) or Geriatric Depression Scale (GDS) suggested depression symptoms over time with no later recovery (BDI > 21 or GDS > 10 at their final timepoint; 7 participants; 32 scans).

Adult lifespan replication sample: One participant was excluded from each of the adult lifespan replication datasets (BETULA and NESDA) based on initial GAMM trajectory analysis of their hippocampal change estimates. Each of these participants had three timepoints. In SI Fig 8 we visualize these outliers for each of their timepoints and their subsequent change estimates. In BETULA data, we show how the removal of the outlier influences the observed PRS-AD-change association by visualizing the association both before and after outlier removal.

AD datasets: After following the procedures described above to determine the AD-control samples, no datapoints were excluded from ADNI or AIBL data.

Replication

To test replication, we used the two remaining longitudinal adult cohorts from the Lifebrain consortium that each had up to three MRI timepoints available: the BETULA project and the Netherlands Study of Depression and Anxiety (NESDA). We tested replication of PRS-AD effects upon change in left and right hippocampus, left and right amygdala, and using the principal component of age-relative change derived from the first 50 AD-accelerated features from our machine learning model (PC1relChange), excluding hippocampal and amygdala volumes. Because the adult lifespan replication sample was statistically less powered to estimate individual specific change due to fewer follow-up observations, these decisions were taken to reduce the number of tests in the replication analysis, and guided by the associations observed in the LCBC discovery sample – currently the most densely sampled MRI dataset for longitudinal lifespan follow-up. We observed replication of both PRS-AD and PRS-ADnoAPOE effects upon left and right hippocampal change, and using the same PRS-ADnoAPOE scores as in the discovery sample. We did not observe replication of PRS-AD effects upon amygdala change, nor upon PC1relChange. We observed a replication of the absolute change trajectory, indicating all healthy individuals lay on a trajectory of accelerated change in AD-accelerated features, with a similar onset of acceleration as in the discovery sample: ~50 years of age.

The ADNI-derived machine learning model was tested in independent AD-control data from AIBL, achieving an AUC of 0.952. Similarly, we demonstrated we could directly apply the ADNI-derived model weights to the independent LCBC discovery sample (adult lifespan change estimates conditional on age) and the prediction was associated with PRS-AD in healthy adults.

Randomization

For the main analysis, randomization is not applicable as there was no group allocation.
ADNI and AIBL participants were assigned to groups based on their diagnosis across timepoints. Participants having an AD diagnosis by their final timepoint were assigned to an AD group (AD-long). Participants consistently classed as healthy across all timepoints were assigned to a normal control group (NC-long).

Blinding

For the main analysis, blinding is not applicable as there was no group allocation.
ADNI and AIBL participant clinical status was decided by a clinical review panel. Blinding may not be applicable for the present study, as the groups tested were defined by longitudinally-derived diagnoses.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.

Magnetic resonance imaging

Experimental design

Design type	T1-weighted anatomical scans
Design specifications	NA
Behavioral performance measures	NA

Acquisition

Imaging type(s)	Structural
Field strength	3T and 1.5T
Sequence & imaging parameters	LCBC; Avanto Siemens 1.5T; TR: 2400 ms, TE: 3.61 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 1.2 mm, FoV: 240×240 m, 160 slices, iPat = 2 LCBC; Avanto Siemens 1.5T; TR: 2400 ms, TE = 3.79 ms, TI = 1000 ms, flip angle = 8, slice thickness: 1.2 mm, FoV: 240 x 240mm, 160 slices LCBC; Skyra Siemens 3T; TR: 2300 ms, TE: 2.98 ms, TI: 850 ms, flip angle: 8°, slice thickness: 1 mm, FoV: 256×256 mm, 176 slices BETULA; Discovery GE 3T; TR: 8.19 ms, TE: 3.2 ms, TI: 450 ms, flip angle: 12°, slice thickness: 1 mm, FOV 250×250 mm, 180 slices NESDA; Phillips 3T; TR: 9 ms; TE: 3.5 ms; slice thickness: 1 mm, FOV: 256 x 256 mm, 170 slices.
Area of acquisition	Whole brain coverage

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	Cortical and subcortical reconstruction was performed with FreeSurfer's longitudinal pipeline (v7.1.0)
Normalization	linear, T1
Normalization template	Talairach
Noise and artifact removal	No manual quality control or editing was done
Volume censoring	Not used (structural scans only)

Statistical modeling & inference

Model type and settings	Generalized additive mixed models; linear models
Effect(s) tested	No tasks or stimulus conditions were used (structural only)

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

Anatomical location(s)	Subcortical ROIs from FreeSurfer, Desikan-Killiany cortical parcellations corresponding to Braak Stages I-III; Desikan-Killiany cortical parcellations covering the whole brain
Statistic type for inference (See Eklund et al. 2016)	FDR-corrected ROI analyses
Correction	FDR-corrected ROI analyses. For PRS-AD effects surviving FDR correction (across 576 PRS-AD tests) we retested the FDR-corrected association after excluding APOE from the polygenic score (PRS-ADnoAPOE). Statistical significance of PRS-ADnoAPOE effects was considered where the number of signifcant PRS-ADnoAPOE effects ($p<.05$) exceeded the 5% false positive rate expected by chance. For replication of PRS-AD and PRS-ADnoAPOE effects, no correction for multiple comparisons was performed. We considered it a replication where the number of significant tests per structure exceeded the 5% false positive rate and the association was FDR-corrected significant in the discovery sample.

Models & analysis

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

Multivariate modeling and predictive analysis

GAMMs modelling age in all FreeSurfer subcortical ROI's (volumes and intensities; aseg atlas) and Desikan-Killiany cortical ROIs (volume, thickness, area, grey/white contrast). In AD-control data, the subject-specific slopes (age-relative change) across all 364 features were used as input to supervised binary machine learning classification using XGBoost. Hyperparameters were chosen using 10-fold cross validation across 500 random combinations of the parameter values specified in the Methods. To reduce the risk of overfitting to the training data and increase generalizability, we selected the final hyperparameters based on the mean AUC obtained across the 500 iterations of 10-fold cross-validation, where each iteration logged the maximum AUC achieved across folds. The model was validated in independent AD-control data from AIBL using area under the curve, sensitivity, specificity, and accuracy metrics. The model was further validated by applying the weights to adult lifespan change estimates (Methods). To perform multivariate analyses, we extracted the feature importance matrix and calculated the principal component of age-relative change across different combinations of the top features for classifying AD patients from controls in adult lifespan data, as detailed in the Results and Methods.