nature portfolio

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Last updated by author(s): Aug 13, 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	NA
Data analysis	NA

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

Human participant data is available upon request through an AIBL EOI mechanism from the corresponding author, CM. The data are not publicly available due to containing information that could compromise the privacy of research participants. The animal data that support the findings of this study are available via the link https://figshare.com/s/4e7f588f527163643c5f.

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	We used the term sex in the current manuscript. AIBL human participants' sexes were determined biologically. Both male and female participants were included. The disaggregated sex data of AIBL human participants can be found in Table 1. The disaggregated sex data of experimental mice can be found in Supplemental Table 1. Age, sex, years of education and APOE genotype of AIBL human participants were used to adjust the biomarkers identified for predicting brain Amyloid beta burden in the current study.
Reporting on race, ethnicity, or other socially relevant groupings	Most of the AIBL participants are Caucasian. In this study, 150 Caucasian human participants were recruited from AIBL study.
Population characteristics	The age, sex, years of education, APOE genotype, and clinical diagnosis were provided in Table 1.
Recruitment	The human participants of the current study were randomly recruited from AIBL. Researchers remained blinded to all clinical and demographic information until the completion of data collection.
Ethics oversight	Both human and animal studies of the current study have been approved by the relevant Institutional Review Boards. See details in Ethical Approval of the main manuscript.

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	The sample size for the human study was determined through power analysis using SPSS, which indicated that a minimum of 150 participants was required to detect an effect size of 0.5 with 80% power at an alpha level of 0.05.
Data exclusions	No data exclusions were necessary, as all collected data met the inclusion criteria.
Replication	The results have been replicated at least two to three times under different experimental conditions, confirming the reproducibility of our findings.
Randomization	150 human participants were randomly recruited from the AIBL study using a computer-generated randomization scheme.
Blinding	Researchers remained blinded to all clinical and demographic information until the completion of data collection to prevent bias in data interpretation and analysis.

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

Antibodies

Antibodies used	Details about the antibodies used in this study, including their suppliers and catalog numbers, can be found in Part D of the Supplementary Information.
Validation	All antibodies were validated using titration tests to confirm their reactivity and specificity.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Source information for the cell lines is provided in Methods of the manuscript.
Authentication	Commercially purchased cell lines such as HT22 and U251 cells have been authenticated by the suppliers. BV2 cells have not been authenticated due to resource limitations.
Mycoplasma contamination	We regularly check for mycoplasma contamination quarterly using the MycoAlert Mycoplasma Detection Kit (Lonza), and no contamination was detected during the study.
Commonly misidentified lines (See ICLAC register)	Not applicable, as all cell lines used were commercially purchased and authenticated.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Information about the strains of mice used in the study is provided in Methods of the manuscript.
Wild animals	Not applicable, as only laboratory animals were used in this study.
Reporting on sex	Both male and female mice were used in this study, and the distribution of sexes among the experimental groups is reported in Supplementary Table 1.
Field-collected samples	Not applicable, as all samples used in this study were derived from laboratory animals.
Ethics oversight	Approval for the animal study was obtained from the Florey Animal Ethics Committees. Details about the ethical approval are provided in Ethical Approval of the main manuscript.

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

Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Sample preparation procedures are detailed in Methods of the main manuscript.
Instrument	Details about the flow cytometer (BD FACSCalibur) used in this study can be found in Methods of the main manuscript.
Software	Information about the software used for data analysis is provided in in Methods of the main manuscript.
Cell population abundance	The abundance of the cell populations, expressed as a percentage of the total, is reported in Results of the main manuscript.
Gating strategy	The gating strategy is outlined in Part C of Supplementary Information.

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	A 3D T1-weighted MRI was obtained for screening and co-registration with the PET images. We used Amyloid-PET imaging data in this study. For the detailed methods, please see reference: Rowe CC, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging 31, 1275-1283 (2010).
Design specifications	See above
Behavioral performance measures	NA

Acquisition

Imaging type(s)	See above
Field strength	See above
Sequence & imaging parameters	See above
Area of acquisition	See above

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	NA
Normalization	NA
Normalization template	NA
Noise and artifact removal	NA
Volume censoring	NA

Statistical modeling & inference

Model type and settings	NA
Effect(s) tested	NA

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

Statistic type for inference (See Eklund et al. 2016)	NA
Correction	NA

Models & analysis

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

Graph analysis: Graphpad Prism was used for data visualisation.