nature portfolio

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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	- ZEN software (ZEISS Image acquisition software, v2.3) - Cellranger (v8.0.1) - mkfastq (built-in function in Cellranger)
Data analysis	- Image J (NIH, v1.52g) and its plugin (Diana) - IMARIS (Bitplane, v9.2) - GraphPad Prism(v10) - Python 3.10.0 - numpy 2.0.2 - pandas 2.2.3 - matplotlib 3.9.2 - collections (built-in module in python) - scanpy 1.10.4 - scvi 1.3.0 - gseapy 1.1.8 - semopy 2.3.11 - pyWGCNA 2.2.1 - statsmodels 0.14.5 - scipy 1.15.2

- scikit-learn 1.6.1
- magic-impute 3.0.0

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

All RNA sequencing raw data used in this study has been deposited into Gene Expression Omnibus (Accession number: GSE292137 / Reviewer Accession Token: adkxwkicxfwrhgl).
snRNAseq data from the HD patients was retrieved from the GEO with accession GSE242197. snRNAseq data from the PSP patients was obtained from CZ CELLxGENE (https://cellxgene.cziscience.com/collections/c53573b2-eff4-4c5e-9ad0-b24d422dfd9b). snRNAseq data from the Tsc2 KO mice was obtained from GSE286912. snRNAseq data from excitatory neurons of ROSMAP cohort was obtained from Synapse portal with accession SYN53694054 and SYN53694068.

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	For snRNA-seq analyses, publicly available human snRNAseq data were obtained from GEO and the Synapse portal. Sex was included as a covariate during SysVI batch-effect correction; gender identity information was not available. Human hippocampal FFPE sections were obtained based on tissue availability from the SNUH Brain Bank. The AD group comprised two male and two female donors, and the non-demented control group comprised three male and one female donor. Sex was not analysed as a biological variable for the FFPE cohort owing to the limited sample size.
Reporting on race, ethnicity, or other socially relevant groupings	For snRNAseq analyses, publicly available human snRNAseq data were obtained from GEO and the Synapse portal. Available race and ethnicity information was included as a covariate during SysVI batch-effect correction. For hippocampal FFPE sections, race and ethnicity information was not available for the brain-bank tissue donors and was not considered in the analyses.
Population characteristics	For snRNA-seq analyses, publicly available human snRNAseq data were obtained from GEO and the Synapse portal. Age was included as a covariate during SysVI batch-effect correction. Human hippocampal FFPE sections were obtained from four donors with AD (69-93 years; post-mortem interval, 5-13 h) and four non-demented donors (60-87 years; post-mortem interval, 5.2-9 h). AD cases showed AD neuropathological change (Thal phase 2-3, tau Braak stage 3-4 and CERAD score 2-3), whereas non-demented donors showed Thal phase 0, tau Braak stage 1-2 and CERAD score 0. These FFPE donor characteristics were not used as covariates or incorporated into the analyses.
Recruitment	Human hippocampal FFPE sections were obtained from the SNUH Brain Bank; we were not involved in donor recruitment. Publicly available human snRNA-seq data were obtained from GEO and the SYNAPSE portal.
Ethics oversight	N/A

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 anticipated effect size was based on findings from relevant previous experiments. This informed our power calculations and the selection of sample sizes that provided adequate statistical power while remaining practically feasible.
Data exclusions	For imaging analyses, potential outliers were identified using Grubbs' test in GraphPad Prism ($\alpha = 0.05$). This objective criterion was applied uniformly across groups to identify values statistically inconsistent with the remaining observations. The exclusion criterion was pre-established before statistical analysis and was not based on experimental outcome. For single nuclues RNA sequencing data analysis, to remove poor quality cells, we used filtering criteria described below.

- mitochondrial RNA fraction > 5%
- minimal detected number of genes < 200
- maximal detected number of genes > 8000
Suspected doublets were also automatically removed by scrublet function in scanpy.

For ROSMAP dataset, we excluded samples from individuals with missing values in their pathological scores such as CERAD score, Braak stage, MMSE score, or age.

Replication

Non-behavioural animal experiments were independently performed in two cohorts, with cohort sizes of at least n = 3 and n = 2 mice per group, respectively. Behavioural experiments were independently performed in three cohorts, each comprising approximately 3-4 mice per group. The reported findings were reproducible across cohorts, and all planned replication attempts were successful.

Randomization

Age-matched male and female mice were randomly assigned to experimental and control groups for all in vivo experiments. As no sex-dependent differences in synapse phagocytosis were detected (Extended Data Fig. 2a-d), data from male and female mice were pooled for subsequent analyses. Brain sections for imaging were selected at random. Human FFPE tissues were obtained from the brain bank based on availability, and publicly available human snRNAseq datasets were analysed observationally; thus, no experimental allocation of human samples was applicable.

Blinding

Investigators were blinded to group allocation during in vivo data collection and analysis, including behavioural testing and imaging acquisition and quantification. Blinding was not applicable to analyses of publicly available snRNAseq datasets because the data and metadata were obtained from public repositories. Relevant metadata were included as covariates during SysVI batch-effect correction but did not determine any experimental allocation.

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

anti-S100b (Abcam ab52642, Synaptic System 287-004, Aves Labs S100B-0020) (1:500), anti-IBA1 (Wako 019-19741, Novus NB100-1028) (1:500), anti-mCherry (Invitrogen M11217, Aves Labs mCherry-0020) (1:1000), anti-vGLUT1 (Millipore AB5905) (1:1000), anti-PSD95 (Invitrogen 51-6900) (1:500), anti-vGAT (Synaptic System 131-004) (1:1000), anti-Gephyrin (Synaptic System 147-008) (1:500), anti-Fos (Cell Signaling 2250S, Synaptic System 226-308, Synaptic System 226-017) (1:500), anti-MEGF10 (Merck ABC10) (1:500), anti-ERBB4 (Abcam ab32375, Cell Signaling 4795T) (1:500), anti-Parvalbumin (Swant GP72) (1:1000), anti-beta amyloid (Biolegend 803001, Cell Signaling 2454S) (1:1000), anti-GFAP (Abcam ab4674) (1:1000), anti-AXL (R&D systems AF854) (1:100), anti-Somatostatin (BMA Biomedicals T-4103) (1:500), anti-VIP (Synaptic System 443-005) (1:500), anti-NeuN (Sigma Aldrich ABN91) (1:500), anti-cleaved Caspase3 (Cell Signaling 9661S) (1:500), anti-TREM2 (R&D systems AF1729) (1:500), anti-HA (Cell Signaling 3724S) (1:500), anti-pS6 (Cell Signaling 2211S) (1:500).
Secondary antibodies: Donkey anti-Goat IgG (H&L) Alexa Fluor 405 (Abcam, ab175665). Donkey anti-Goat IgG (H+L) Alexa Fluor 488 (Jackson Laboratory, 705-545-003). Donkey anti-Chicken DyLight 405-conjugated AffiniPure. Donkey Anti-Chicken IgY (IgG) (H+L) (Jackson Laboratory, 703-475-155). Donkey anti-Chicken IgG (H+L) Alexa Fluor 488 (Jackson Laboratory, 703-545-155). Donkey anti-Chicken IgG (H+L) Alexa Fluor 594 (Jackson Laboratory, 709-585-155). Donkey anti-rat IgG (H+L) Alexa Fluor 594 (Invitrogen, A-21209). Donkey anti-rat IgG (H&L) Alexa Fluor 647 (Abcam, ab150155). Donkey anti-rabbit IgG (H&L) Alexa Fluor 405 (Abcam, ab175649). Donkey anti-rabbit IgG (H+L) Alexa Fluor 488 (Invitrogen, A-21206). Donkey anti-rabbit IgG (H+L) Alexa Fluor 594 (Invitrogen, A-21207). Donkey anti-guinea pig IgG (H+L) Alexa Fluor 488 (Jackson Laboratory, 706-545-148). Donkey anti-guinea pig IgG (H+L) Alexa Fluor 594 (Jackson Laboratory, 706-585-148). Donkey anti-guinea pig IgG (H+L) Alexa Fluor 647 (Jackson Laboratory, 706-605-148). Donkey Anti-Sheep IgG H&L (Alexa Fluor® 488) (Abcam, ab150177). Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 594 (Invitrogen, A-21203). All Alexa Fluor 488-conjugated secondary antibodies were used at a dilution of 1:1,000, whereas all other secondary antibodies were used at 1:500.

Validation

anti-S100b (Abcam ab52642): supported by several references including PubMed: 38082296
anti-S100b (Synaptic System 287-004): verified through ICC/IHC experiment by manufacturer
anti-S100b (Aves Labs S100B-0020): verified through ICC/IHC experiment by manufacturer
anti-IBA1 (Wako 019-19741): supported by several references including PubMed: 33361813
anti-IBA1 (Novus NB100-1028): supported by several references including PubMed: 33361813
anti-mCherry (Invitrogen M11217): verified through ICC/IHC experiment by manufacturer

anti-mCherry (Aves Labs mCherry-0020): verified through ICC/IHC experiment by manufacturer
anti-vGLUT1 (Millipore AB5905): supported by several references including PubMed: 33361813
anti-PSD95 (Invitrogen 51-6900): supported by several references including PubMed: 33361813
anti-vGAT (Synaptic System 131-004): supported by several references including PubMed: 33361813
anti-Gephyrin (Synaptic System 147-008): supported by several references including PubMed: 33361813
anti-Fos (Cell Signaling 2250S): verified through ICC/IHC experiment by manufacturer
anti-Fos (Synaptic System 226-308): verified through ICC/IHC experiment by manufacturer
anti-Fos (Synaptic System 226-017): verified through ICC/IHC experiment by manufacturer
anti-Megf10 (Merck ABC10): verified through ICC/IHC experiment by manufacturer
anti-ErbB4 (Abcam ab32375): supported by several references including PubMed: 28230865
anti-ErbB4 (Cell Signaling 4795T): verified through ICC/IHC experiment by manufacturer
anti-Parvalbumin (Swant GP72): supported by several references including PubMed: 36199089
anti-beta amyloid (Biolegend 803001): verified through ICC/IHC experiment by manufacturer
anti-beta amyloid (Cell Signaling 2454S): verified through ICC/IHC experiment by manufacturer
anti-GFAP (Abcam ab4674): supported by several references including PubMed: 33361813
anti-Axl (R&D systems AF854): verified through ICC/IHC experiment by manufacturer
anti-Somatostatin (BMA Biomedicals T-4103): verified through ICC/IHC experiment by manufacturer
anti-VIP (Synaptic System 443-005): verified through ICC/IHC experiment by manufacturer
anti-NeuN (Sigma Aldrich ABN91): verified through ICC/IHC experiment by manufacturer
anti-cleaved Caspase3 (Cell Signaling 9661S): verified through ICC/IHC experiment by manufacturer
anti-TREM2 (R&D systems AF1729): verified through ICC/IHC experiment by manufacturer
anti-HA (Cell Signaling 3724S): verified through ICC/IHC experiment by manufacturer
anti-pS6 (Cell Signaling 2211S): verified through ICC/IHC experiment by manufacturer

Donkey anti-Goat IgG (H&L) Alexa Fluor 405 (Abcam, ab175665)
Donkey anti-Goat IgG (H+L) Alexa Fluor 488 (Jackson Laboratory, 705-545-003)
Donkey anti-Chicken DyLight 405-conjugated AffiniPure Donkey Anti-Chicken IgY (IgG) (H+L) (Jackson Laboratory, 703-475-155)
Donkey anti-Chicken IgG (H+L) Alexa Fluor 488 (Jackson Laboratory, 703-545-155)
Donkey anti-Chicken IgG (H+L) Alexa Fluor 594 (Jackson Laboratory, 709-585-155)
Donkey anti-rat IgG (H+L) Alexa Fluor 594 (Invitrogen, A-21209)
Donkey anti-rat IgG (H&L) Alexa Fluor 647 (Abcam, ab150155)
Donkey anti-rabbit IgG (H&L) Alexa Fluor 405 (Abcam, ab175649)
Donkey anti-rabbit IgG (H+L) Alexa Fluor 488 (Invitrogen, A-21206)
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Donkey anti-guinea pig IgG (H+L) Alexa Fluor 594 (Jackson Laboratory, 706-585-148)
Donkey anti-guinea pig IgG (H+L) Alexa Fluor 647 (Jackson Laboratory, 706-605-148)
Donkey Anti-Sheep IgG H&L (Alexa Fluor® 488) (Abcam, ab150177)
Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 594 (Invitrogen, A-21203)

All stated secondary antibodies were verified through IHC experiment by manufacturer.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	HEK293T cells were originally obtained from ATCC
Authentication	HEK293T cells have been maintained in our laboratory for an extended period and were not independently authenticated for this study.
Mycoplasma contamination	HEK293T cell line was confirmed for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell line was used in this study.

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	All animal experiments used Mus musculus: C57BL/6J wild-type mice and C57BL/6J-background APP/PS1 and 5XFAD transgenic mice. APP/PS1 and 5XFAD mice were maintained by breeding with C57BL/6J mice. Both male and female mice were used; as no sex-dependent differences in synapse phagocytosis were detected (Extended Data Fig. 2a-d), data from both sexes were pooled for subsequent analyses. APP/PS1 mice aged 3-18 months, 5XFAD mice aged 2-10 months, and age-matched C57BL/6J wild-type controls were used as indicated for each experiment. For snRNAseq, 2-month-old 5XFAD and 3-month-old 5XFAD and wild-type mice were used. Mice were housed under standard conditions on a 12-h light-dark cycle at 22°C and 30% relative humidity, with food and water provided ad libitum.
Wild animals	No wild animals were used in this study.
Reporting on sex	In Extended Data Fig. 2a-d, we confirmed sex difference does not affect phenotype of interest. Therefore, we used both male and female randomly for other experiments.

Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	All mouse experiments were performed according to articles approved by Institutional Animal Care and Use Committees (IACUC) protocols from Korea Advanced Institute of Science and Technology (KAIST).

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A