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Corresponding author(s): Xinglu Huang, Hui Wang, Yijin Liu

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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	*Provide a description of all commercial, open source and custom code used to collect the data in this study, specifying the version used OR state that no software was used.*
Data analysis	The following software packages were used in this study: Rosetta 2022.45 for docking analysis of the Aβ3FTn-Aβ complex, with LigPlus v2.3 used for docking interface analysis; GROMACS 2024.4 for molecular dynamics simulations; PyMOL 3.1 for structural visualization; AutoDock 4.2.6 and AutoDock Tools 1.5.7 for docking analysis of the Aβ3FTnAu-Aβ interaction model; Biacore T200 Evaluation Software v3.2 for surface plasmon resonance analysis; ImageJ 1.53t/FIJI for image quantification and three-dimensional image preprocessing; Imaris 9.0.1 for three-dimensional reconstruction and analysis of light-sheet images; ANY-maze v7.16 for behavioral maze analysis; Proteome Discoverer v2.5 for proteomic data processing of protein adsorption analyses; DIALS 3.6.2, Phaser 2.8.3 and the PHENIX software suite 1.20.1-4487 for crystallographic data processing, molecular replacement and structural refinement, respectively; Cell Ranger v6.1.2 for processing raw single-cell RNA-seq data to generate expression matrices, and Seurat v4.3.0.1, Harmony, CellChat v1.6.1, clusterProfiler v4.6.2 and GSVA v1.46.0 for downstream single-cell RNA-seq analysis; and GraphPad Prism 10.5.0 for statistical analysis.

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 crystallographic coordinates and structure factors have been deposited in the PDB under accession codes 9W28, 9W29 and 9W2A. The raw X-ray diffraction data for the crystal structures have been deposited in Zenodo at https://doi.org/10.5281/zenodo.20263578. The mass spectrometry proteomics data have been deposited in the ProteomeXchange Consortium via the iProX partner repository under accession code PXD078546. The single-cell RNA sequencing data generated in this study have been deposited in the Gene Expression Omnibus (GEO) under accession number GSE324517. The authors declare that data supporting the findings of this study are available within the article and its Supplementary Information. Source data are provided with this paper.

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	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used.* *Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected.* *Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status).* *Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.)* *Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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	Sample sizes were determined based on previous experience and relevant literature for each specific experiment. No statistical methods were used to pre-determine sample sizes.
Data exclusions	No animals were excluded from the analyses. Data were excluded only according to predefined technical quality-control criteria for single-cell RNA-seq and proteomic analyses.
Replication	Experiments were repeated independently where applicable. Sample sizes and replicate numbers are provided in the figure legends and Methods.
Randomization	The experimental groups were allocated randomly.

Blinding	Behavioural and histological analyses were performed by investigators blinded to group allocation. Quantification of confocal and light-sheet images, behavioral testing data, dendritic spine analysis, and histological image analyses was performed by investigators blinded to group allocation. Single-cell RNA-seq data were analysed after de-identification of the samples.

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	The antibodies and working dilutions were as follows: anti-β-amyloid antibody 6E10 (BioLegend, 803015; 1:1,000 for immunofluorescence and dot blot), anti-amyloid fibrils OC antibody (StressMarq, SPC-507; 1:1,000 for dot blot and 1:100 for immunofluorescence), anti-oligomer A11 polyclonal antibody (Invitrogen, AHB0052; 1 μg/ml), anti-NMDAR2A antibody (Abcam, ab169873; 1:1,000 for Western blot), PSD95-specific antibody (Proteintech, 81106-1-RR; 1:5,000 for Western blot), anti-synaptophysin antibody (Abcam, ab52636; 1:1,000 for Western blot), ApoE antibody (Proteintech, 66830-1-Ig; 1:3,000 for Western blot and 1:500 for immunofluorescence), Trem2 monoclonal antibody (Cell Signaling Technology, 76765; 1:1,000 for Western blot), Trem2 antibody (Affinity Biosciences, DF12529; 1:500 for immunofluorescence), PSD95 monoclonal antibody (Affinity Biosciences, BF8419; 1:300 for immunofluorescence), and PE-conjugated anti-mouse CD31 antibody (BioLegend, 102508; 1:500 for immunofluorescence).
Validation	All antibodies used in this study were commercially obtained and validated by the manufacturers. Detailed product information and validation data are available on the manufacturers' official websites, as listed below. anti-β-amyloid antibody 6E10 (BioLegend, 803015): https://www.biolegend.com/en-gb/products/anti-beta-amyloid-1-16-antibody-10998 anti-amyloid fibrils OC antibody (StressMarq, SPC-507): https://www.stressmarq.com/products/antibodies/polyclonal-antibodies/amyloid-fibrils-oc-antibody-spc-507/ anti-oligomer A11 polyclonal antibody (Invitrogen, AHB0052): https://www.thermofisher.com/antibody/product/Oligomer-A11-Antibody-Polyclonal/AHB0052 anti-NMDAR2A antibody (Abcam, ab169873): https://www.abcam.com/en-us/products/primary-antibodies/nmdar2a-antibody-ab169873 PSD95-specific antibody (Proteintech, 81106-1-RR): https://www.ptglab.com/products/PSD95-Specific-DLG4-Antibody-81106-1-RR.htm anti-synaptophysin antibody (Abcam, ab52636): https://www.abcam.com/en-us/products/primary-antibodies/synaptophysin-antibody-ep1098y-synaptic-marker-ab52636 ApoE antibody (Proteintech, 66830-1-Ig): https://www.ptglab.com/products/APOE-Antibody-66830-1-Ig.htm Trem2 monoclonal antibody (Cell Signaling Technology, 76765): https://www.cellsignal.com/products/primary-antibodies/trem2-e7p8j-rabbit-mab-carboxy-terminal-antigen/76765 Trem2 antibody (Affinity Biosciences, DF12529): https://www.affbiotech.com/goods-15841-DF12529-TREM2_Antibody.html PSD95 monoclonal antibody (Affinity Biosciences, BF8419): https://www.affbiotech.com/goods-20975-BF8419-PSD95_Mouse_Monoclonal_Antibody.html PE-conjugated anti-mouse CD31 antibody (BioLegend, 102508): https://www.biolegend.com/ja-jp/products/pe-anti-mouse-cd31-antibody-379?GroupID=BLG5721

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	PC-12 cells (CRL-1721.1) and bEnd.3 cells (CRL-2299) were purchased from the American Type Culture Collection (Manassas, USA). Mouse primary hippocampal neurons (CP-M107) were purchased from Procell Life Science & Technology Co., Ltd.
Authentication	Cell lines were not authenticated.
Mycoplasma contamination	The cell lines regularly tested for mycoplasma contamination, and no mycoplasma contamination was found.

Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines are 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	The study used 5×FAD transgenic mice and wild-type C57BL/6J mice. The 5×FAD mice were obtained from The Jackson Laboratory, and 6-month-old mice were used for the in vivo therapeutic studies. Age-matched wild-type littermates were used as controls where applicable. Additional wild-type C57BL/6J and Kunming mice were used for safety and pharmacokinetic-related experiments, as described in the Methods.
Wild animals	The study did not involve wild animals.
Reporting on sex	Both male and female mice were included in experiments in which sex could influence the outcome, such as behavioural assessments and evaluation of therapeutic efficacy. Sex was balanced between groups, or mice of the same sex were used within an individual experiment to minimize sex-related variability.
Field-collected samples	No field collected samples were involved in this study.
Ethics oversight	All animal experiments were approved by the Animal Ethics Committee of Hebei University of Technology (HEBUTacuc2023010) and Nankai University (2024-SYDWLL-000198).

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

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.*