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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	ImageStudio software version 5.2.5 (LI-COR); Compass software version 4.0.0 (ProteinSimple); StepOne software version 2.1 (Applied Biosystems).
Data analysis	ImageStudio software version 5.2.5 (LI-COR); ImageJ/FjJi software version 2.0.0.-rc-67/1.52c; Photoshop CS5 version 12.0.1 (Adobe); Illustrator version 23.0.6 (Adobe); Imaris Version 9 (Oxford Instruments); Compass software version 4.0.0 (ProteinSimple); Biolayout express 3D version 3.3; Advanced Analysis 2.0.115 software package; Cytoscape version 3.6.1; Partek Genomics Suite software version 6.6 and 7.18; Interferome data base version 2.01; STRING version 11.0; GraphPad Prism software version 7.0c; StepOne software version 2.1 (Applied Biosystems).

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/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

All data generated and/or analyzed during this study are either included in this article (and its supplementary information files) or are available from the corresponding author on reasonable request.

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	All cell culture experiments requiring statistical analysis were performed at least 3 times as indicated in the figure legends. Power analysis was used to predetermine the sample size in case of in vivo studies. For animal experiments requiring statistical analysis we used at least 5 animals per group with the exception of only 3 animals in the 3 months old WT group used for NanoString analysis. See specific figure legends and extended data figure legends for details.
Data exclusions	All animals were healthy and generated specifically for the experiments described. Animals or samples were excluded from analysis only in the instance of technical failure.
Replication	All experiments were performed with at least three independent biological samples. All attempts at replication were successful.
Randomization	The animals were littermates, and inbred lines were used, where the individual mice were identical, therefore no specific randomization was needed. Mice were grouped according to genotype before they were randomly assigned to the experimental conduct (e.g. Morris Water Maze test).
Blinding	All researchers performing animal experiments and/or data analysis were blinded. However, cell culture treatments and analyses were mostly performed by the same individual, so blinding was not always possible. Wherever possible, a second researcher blinded to the analysis confirmed the result.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	For tissue stainings, anti-biotinylated AT8 (Thermo Fisher Scientific, MN1020B, lot SB2334646, 1:500), anti-Iba1 (Wako, 019-19741, lot PTE0555, 1:400 and Abcam, ab5076, lot GR3245261-1, 1:1500), anti-GFAP (Invitrogen, 13-0300, lot SA247423, 1:100) and anti-pTau-S416 (Abcam, ab119391, lot GR93695-21, 1:1000) were used. For immunoblot analysis, the following antibodies were used: anti-Tau5 (Thermo Fisher Scientific, MA5-12808, lot sc2348223, 1:500), anti-MC1 (gift from P. Davies, New York, USA, 1:1000), anti-PHF-1 (gift from P. Davies, New York, USA, 1:1000), anti-Caspase-1 (Genentech, clone 4B4.2.1, gift from Genentech, San Francisco, CA, 1:1000; Adipogen, clone Bally-1, AG-20B-0048, lot 26101409, 1:1000; Adipogen, clone Casper-1, AG-20B-0042, lot A28881708, 1:50), anti-IL-1beta (Gene Tex, GTX74034, lot 42900, 1:1000), anti-ASC (Adipogen, clone Alz177, AG-25B-0006, lot A40221902, 1:1000), anti-β-actin (Cell Signaling, 4967, lot 11, 1:2000), anti-pCaMKIIα (Cell Signaling, clone D21E4, 12716T, 1:1000), anti-CaMKIIα (Cell Signaling, clone 6G9, 50049S, lot 1, 1:1000), anti-pGSK-3β (BD, clone 13A, 612313, lot 3768, 1:1000), anti-GSK-3β (Cell Signaling, clone 27C10, 9315S, lot 14, 1:1000), anti-p25/p35 (Cell Signaling, clone C64B10, 2680S, lot 5, 1:1000), anti-demPP2A (Merck Millipore, clone 4b7, 05-577, lot 3154938, 1:500), anti-PP2A subunit C (Cell Signaling, clone 52F8, 2259T, lot 2 1:1000) and anti-PME-1 (Merck Millipore, 07-095, lot 2805155, 1:1000). For analysis on the Jess system from ProteinSimple, anti-Caspase-1 (Adipogen, clone Casper-1, AG-20B-0042, lot A28881708, 1:50) was used.
Validation	PHF-1 and MC1 antibodies from Peter Davies are validated for immunoblot analysis several times and widely used in the field. See e.g. Götz et al (2001) Science Aug 24;293(5534):1491-5, Bhaskar et al (2010) Neuron 6;68(1):19-31 and Li and Cho (2019) J Neurochem doi: 10.1111/jnc.14830. Caspase-1 clone 4b4.2.1 from Genetech was validated by using tissue from Caspase-1-

knockout mice. Validation data for commercial antibodies are available on vendor websites. Positive controls were included in every experimental run whereever possible to ensure accurate function of each antibody.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	THY-Tau22 transgenic (Schindowski et al., Am J Pathol 2006), ASC-/- (Millenium Pharmaceuticals, Cambridge, MA, USA) and NLRP3-/- mice (Millenium Pharmaceuticals, Cambridge, MA, USA), all on C57BL/6 genetic background, were used. Male and female animals at the age of 3, 8 and 11 months were used.
Wild animals	Study did not involve wild animals.
Field-collected samples	Study did not involve samples collected from the field.
Ethics oversight	Animal care and handling was performed as approved by the local ethical committees (LANUV NRW 84-02.04.2017.A226).

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Post mortem brain material from histologically confirmed AD and FTD cases as well as age-matched controls that had died from non-neurological disease, were derived from the Neurological Tissue Bank of the Biobank of the Hospital Clínic-IDIBAPS. Postmortem times across all cases varied from 6-16,5 hrs. After explantation brain specimen were immediately snap frozen and stored at -80°C until further use. Patients and controls were males and females, 62 ±10 yrs old.
Recruitment	Participants were recruited by the Neurological Tissue Bank of the Biobank of the Hospital Clínic-IDIBAPS.
Ethics oversight	Patients gave their consent to the Biobank of the Hospital-clinic-IDIBAPS. Ethic approval was obtained by the Biobank.

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