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	Any software was not used in the data collection.
Data analysis	Adobe Photoshop (Ver 22.0) and Image J (Ver 1.41) were used for image analysis. Prism (Ver 7) and Excel (Ver 16.16.27) were used for data 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 authors declare that all data supporting the finding of this study are available within the article and Source Data files.

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	Generally sample size was chosen empirically, based on prior experience of how big a sample size must be to most probably obtain a reproducible, statistically significant result.
Data exclusions	No data were excluded.
Replication	All representative data and images were obtained from at least three biological independent experiments with similar results.
Randomization	For each mouse line, mice were randomly selected from available pools of mice within each group. No other randomization is applicable for this study.
Blinding	Investigators were blinded to the group allocation during the data collection and blinded to sample identity for the analysis of immunohistochemistry and western blotting.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	Tau5 (Santa Cruz, SC-58860), AT-8 (Thermo Fisher Scientific, MN1020), beta-actin (Sigma-Aldrich, A5316), AEP (Cell signaling, 93627S), T22 (Millipore, ABN454), Tau N368 (custom antibody, Zhang Z, et al. Nat Med, 2014), and Tau K353-DOPEGAL (custom antibody), Dopamine beta-hydorxylase (DBH) antibody (Invitrogen, PA3-925). Tau5, beta-actin, 1:1500 dilution; AT-8, T22, DBH, 1:500 dilution; Tau N368, Tau K353-DOPEGAL, AEP, 1:1000 dilution.
Validation	All antibodies were verified in mice tissue, human cell line, and primary culture cell by western blotting to ensure that the antibody binds to the antigen stated. Custom-made TauK353-DOPEGAL antibody was verified in mice brain sections by immunohistochemistry (Figure 4A), in Tau transgenic mice by western blotting (Figure 4B), and in vitro by Ab epitope peptide (Figure 4C).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293 cells and SH-SY5Y (CRL-2266TM) neuroblastoma cells were purchased from ATCC.
Authentication	HEK293 cells and SH-SY5Y cells were authenticated using short tandem repeat (STR) profiling by ATCC 135-XV.
Mycoplasma contamination	No mycoplasma was detected in the used cell lines.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell line were used.

Animals and other organisms

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

Laboratory animals	The AEP knockout mice on a mixed 129/Ola and C57BL/6 background (3-month-old Female mice). Tau P301S (strain# 008169), MAPT (Strain# 005491), and C57BL/6J (strain# 000664) were purchased from Jackson Laboratory. As described in Methods section, 3-month-old female mice were used for the experiments. Temperatures of 18-23 C with 40-60% humidity and 12 light/12 dark cycle were used for housing condition.
Wild animals	No wild animals were used in the study.
Field-collected samples	No field-collected samples were used in the study.
Ethics oversight	Animal care and procedures were conducted according to the National Institutes of Health Guide for Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee at Emory University. (PROTO201700326)

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	LC sections from 10 postmortem AD cases of Braak stages IV-VI (5 males and 5 females, age 62 ± 10.9 years, mean ± SD) and 10 cognitively normal controls (6 males and 4 females, age 59.4 ± 8.8 years, mean ± SD) were used. The standardized diagnostic criteria of CERAD (Consortium to Establish a Registry for AD) was used for the evaluation and diagnosis of patients with AD.
Recruitment	Brain sections from postmortem AD (10) patients and controls (10) were obtained from the Emory Goizueta Alzheimer's Disease Research Center.
Ethics oversight	Informed consent was obtained from the subjects prior to death.

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