

## 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

- |                                     |                                     |  |
|-------------------------------------|-------------------------------------|--|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of all covariates tested   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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) |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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

Western blot: Immuno-reactive bands were scanned with a LAS-3000mini LuminolImage analyzer (Fuji Film), and band intensity was analyzed by Image Studio Digits (LI-COR Bioscience). Immunohistochemistry and Duolink: The sections were scanned on a NanoZoomer NDP system (Hamamatsu Photonics), and signals were quantified using Definiens Tissue Studio (Definiens). MRI: The hippocampal volume of each mouse was calculated using ImageJ software.

Data analysis

All analyses were completed with Graphpad Prism7 Software (San Diego, CA, USA). Differences between groups were examined for statistical significance with Student's t-test.

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

The datasets generated during and/or analyzed during the current study 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](https://www.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 sized use in this study are appropriate. We carried out the experiments using 3 or more samples per group.
Data exclusions	There is no data exclusions in this study.
Replication	We confirmed reproducibility by multiple independent data collections.
Randomization	Randomization is not relevant to our study. We did not chose samples from among many, but used all samples for experiments.
Blinding	The investigators were not blinded during data collection, because first author carried out both designing of experiments and quantitative assessments. However, two or more persons agree with the interpretation of experimental data.

## 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   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines                  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology                          |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Animals and other organisms |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Human research participants            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |

### Methods

- |                                     |  |
|-------------------------------------|--|
| n/a                                 | Involved in the study                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> MRI-based neuroimaging |

## Antibodies

### Antibodies used

CAPON (WB, IHC): Santa Cruz #sc374504(clone C9)  
 CAPON(Duolink): Santa Cruz #sc9138 (clone R300)  
 GFP: Abcam #ab6673  
 APP/A $\beta$ : Merck Millipore #MAB348 (clone 22c11) A $\beta$ : Saido et al, J. Biol. Chem, 1994 (N1D)  
 Tau5 (total Tau): Thermo #AHB0042 (Tau5)  
 AT8 (pS202/pT205-Tau): Innogenetics #90206 (anti PHF-TAU)  
 PHF1 (pS396/pS404-Tau): kindly provided by Peter Davis  
 pS396-Tau: Covance #MMS-546R  
 pS404-Tau: Abcam #ab92676  
 pS422-Tau: Covance #PRB-524P  
 pY18-Tau: Covance #SIG-39436-200  
 pY29-Tau: Covance #SIG-39439-200  
 Iba1: Wako #NCNP24  
 GFAP: Merck Millipore #MAB3402  
 nNOS: CST #42315  
 NeuN: Abcam #ab104224  
 cleaved-caspase3: CST #9661S  
 CytC: CST #4272S  
 Dexas1: Abcam #ab171370  
 Bax: Abcam #ab32503  
 p-ERK: CST #4695  
 ERK: CST #9102  
 p-MEK: CST #9121  
 MEK: CST #9122  
 $\beta$ -actin: SIGMA #A5443

nature research | reporting summary October 2018

Tau13(human Tau):Santa Cruz #sc-21796  
 RD3:Merck Millipore #05-803  
 RD4:MyBiosource #MBS604301  
 GSDMD:Abcam #ab209845  
 GSDME:Abcam #ab215191  
 Olig2:Abcam #ab109186  
 CD31: Abcam #ab28364  
 Synaptophysin:PROGEN #61412  
 VGAT:Synaptic Systems #131002  
 MAP2:Leinoco Technologies #M119  
 MC1:kindly provided by Peter Davis

Validation

CAPON: WB (1:2500), IHC (1:1000)  
 CAPON: Duolink (1:500)  
 GFP: WB (1:5000), IHC (1:1000)  
 APP/A $\beta$ : IHC (1:2500)  
 A $\beta$ (N1D): IHC (1:500)  
 Tau5 (total Tau)(Tau5): WB (1:2500)  
 AT8: WB (1:2500), IHC (1:200)  
 PHF1: WB (1:2500)  
 pS396-Tau: WB (1:2500)  
 pS404-Tau: WB (1:2500)  
 pS422-Tau: WB (1:2500)  
 pY18-Tau: WB (1:1000)  
 pY29-Tau: WB (1:1000)  
 Iba1: IHC (1:200)  
 GFAP: IHC (1:200)  
 nNOS: WB (1:2500), IHC (1:200)  
 NeuN: IHC (1:500)  
 cleaved-caspase3: IHC (1:200)  
 CytC: IHC (1:200), WB (1:1000)  
 Dexas1: WB (1:5000)  
 Bax: WB (1:2500)  
 p-ERK: WB (1:1000)  
 ERK: WB (1:2500)  
 p-MEK: WB (1:2500)  
 MEK: WB (1:2500)  
 $\beta$ -actin: WB (1:5000)  
 Tau13 (human Tau): WB (1:2500 )  
 RD3 Merck Millipore: WB (1:1000)  
 RD4 MyBiosource: WB (1:1000)  
 GSDMD: WB (1:1000)  
 GSDME :WB (1:1000)  
 Olig2: IHC (1:1000)  
 CD31: IHC (1:200)  
 Synaptophysin: IHC (1:50)  
 VGAT Synaptic Systems: IHC (1:1500)  
 MAP2: IHC (1:1000)  
 MC1: IHC (1:200)

## Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals

All animal experiments were conducted in accordance with the guidelines of the RIKEN Center for Brain Science. All strains were maintained on a C57BL/6 background. Sex and age of mice used in each experiments were described in figure legends.

Wild animals

No wild animals were used

Field-collected samples

No field-collected samples were used

Ethics oversight

All animal experiments were conducted in accordance with the guidelines of the RIKEN Center for Brain Science.

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

## Magnetic resonance imaging

Experimental design

Design type

Resting state

Design specifications

Behavioral performance measures

### Acquisition

Imaging type(s)

Field strength

Sequence & imaging parameters

Area of acquisition

Diffusion MRI  Used  Not used

### Preprocessing

Preprocessing software

Normalization

Normalization template

Noise and artifact removal

Volume censoring

### Statistical modeling & inference

Model type and settings

Effect(s) tested

Specify type of analysis:  Whole brain  ROI-based  Both

Statistic type for inference   
(See [Eklund et al. 2016](#))

Correction

### Models & analysis

n/a | Involved in the study

Functional and/or effective connectivity

Graph analysis

Multivariate modeling or predictive analysis