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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	ImageJ was used for western blot quantification and TUNEL % calculations
Data analysis	Prism 6.0 was used for all statistical assessments.

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 upon request. 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 source data and exact P values (if applicable) for every figure are included in the supporting information that accompanies the paper.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We note that no power calculations were used. Sample sizes are based on previously published experiments where differences were observed.
Data exclusions	No samples were excluded from the analysis.
Replication	Results shown are representative of several independently performed experiments. Number of biological replicates is as described in figure legends.
Randomization	Treatment groups were randomly assigned to mice at weaning age.
Blinding	Investigators were blinded to allocation during experiments and outcomes assessment, except for rare instances where blinding was not possible.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	There are no restrictions.

Antibodies

Antibodies used	Western Blot - Total Tau - (ThermoFisher, MN1000; clone:n/a; lot:QC214397; 1:5000) Western Blot - Phospho-tau S202/T205 - (ThermoFisher, MN1020; clone:n/a ; lot:QJ20872020; 1:1000) IHC - Phospho-tau S202/T205 - (ThermoFisher, MN1020; clone:n/a; lot:QJ20872020; 1:500) IHC - Phospho-tau T231 - (ThermoFisher, MN1040; clone:AT180; lot:SL2484202; 1:500) IHC - Phospho-tau S396 - (Abcam, 109390; clone: n/a; lot:GR303639-17; 1:500) IHC - Gfap - (Dako, Z0334; clone:n/a; lot:20010594; 1:500) IHC - Iba1 - (Novus, NB100-1028; Lot#S7C5 E210518; Clone# n/a; 1:100) IF - NeuN - (EMD, MAB377; clone:n/a; lot:2987527; 1:200) IF - Cd11b - (BioRad, MCA711G; clone:n/a; lot:1709; 1:500) IF - Gfap - (Dako, Z0334; clone:n/a; lot:20010594; 1:500) IF - DAPI - (Invitrogen, D1306; clone:n/a; lot:1836282; 1:1000) IF - Goat anti-Rat AlexaFluor 594 - (Invitrogen, A-11007; clone:n/a; lot:1903506; 1:500) IF - Iba1 - (Wako, 019-19741; clone:n/a; lot:LKH4161; 1:500) FACS IF - LIVE/DEAD Aqua - (Invitrogen, L34966; clone:n/a; lot:1899019; 1:250) FACS IF - Cd11b eFluor 450 - (eBioscience, 48-0112-80; clone:M1/70; lot:4306306; 1:100) FACS IF - Cd45 APC eFluor 780 - (eBioscience, 47-0451-82; clone:30-F11; lot:E10101-1636; 1:200)

FACS IF - Glast1 PE - (Miltenyi Biotec, 130-095-821; clone:n/a; lot:5160331127; 1:100)
FACS IF - O1 AF 700 - (R&D Systems, FAB1327N-100UG; clone:n/a; lot:1474296; 1:100)
FACS IF - Cd56 APC (R&D Systems, FAB7820A; clone:n/a; lot:ADIK0117051; 1:100)

Validation

All antibodies are from commercially available sources and have been validated from the manufacturer with supporting publications found on manufacturer websites. See below for summary:
Western Blot - Total Tau - (ThermoFisher; MN1000)
Species: Bovine, Rat, Non-human primate, Human, Mouse
Application: ELISA, Immunocytochemistry, Immunofluorescence, Immunohistochemistry, Western Blot
Western Blot - Phospho-tau S202/T205 - (ThermoFisher, MN1020)
Species: Chicken, Dog, Fruit fly, Hamster, Human, Mouse, Non-human primate, Rabbit, Rat
Application: ELISA, Immunocytochemistry, Immunofluorescence, Immunohistochemistry, Western Blot

IHC - Phospho-tau S202/T205 - (ThermoFisher, MN1020)
Species: Chicken, Dog, Fruit fly, Hamster, Human, Mouse, Non-human primate, Rabbit, Rat
Application: ELISA, Immunocytochemistry, Immunofluorescence, Immunohistochemistry, Western Blot
IHC - Phospho-tau T231 - (ThermoFisher, MN1040)
Species: Cat, Chicken, Dog, Fruit fly, Hamster, Horse, Human, Mouse, Non-human primate, Rabbit, Rat
Application: Immunofluorescence, Immunohistochemistry, Western Blot
IHC - Phospho-tau S396 - (Abcam, 109390)
Species: Mouse, Rat, Human
Application: Dot blot, Immunohistochemistry, Western Blot
IHC - Gfap - (Dako, Z0334)
Species: Cat, Cow, Dog, Mouse, Rat, Sheep
Application: Immunohistochemistry, Immunofluorescence
IHC - Iba1 - (Novus, NB100-1028)
Species: Human, Mouse, Rat, Porcine
Application: Western Blot, Immunohistochemistry, Immunofluorescence, ELISA
IF - NeuN - (EMD, MAB377)
Species: Human, Rat, Mouse, Ferret, Chick and Salamander
Application: Immunohistochemistry, Immunofluorescence, Immunoblotting
IF - Cd11b - (BioRad, MCA711G)
Species: Mouse, Human
Application: Flow Cytometry, Immunohistology, Immunoprecipitation Immunofluorescence
IF - Gfap - (Dako, Z0334)
Species: Cat, Cow, Dog, Mouse, Rat, Sheep
Application: Immunohistochemistry, Immunofluorescence
IF - DAPI - (Invitrogen, D1306)
Species: Nucleic Acid
Application: Immunofluorescence
IF - Goat-anti-Rat AlexaFluor 594 (Invitrogen, A-11007)
Species: N/A
Application: Flow Cytometry, Immunohistochemistry, Immunofluorescence
IF - Iba1 - (Wako, 019-19741)
Species: Rat, Mouse
Application: Immunohistochemistry, Immunofluorescence, Western Blot
FACS IF - LIVE/DEAD Aqua - (Invitrogen, L34966)
Species: Eukaryotic Cells
Application: Flow Cytometry
FACS IF - Cd11b eFluor 450 - (eBioscience, 48-0112-80)
Species: Mouse, Human
Application: Flow Cytometry
FACS IF - Cd45 APC eFluor 780 - (eBioscience, 47-0451-82)
Species: Mouse, Human
Application: Flow Cytometry
FACS IF - Glast1 PE - (Miltenyi Biotec, 130-095-821)
Species: Human, Mouse, Rat
Application: Flow Cytometry, Immunofluorescence
FACS IF - O1 AF 700 - (R&D Systems, FAB1327N)
Species: Human, Mouse, Rat, Chicken
Application: Flow Cytometry
FACS IF - Cd56 APC (R&D Systems, FAB7820A)
Species: Mouse
Application: Flow Cytometry

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Primary astrocyte and microglia cultures generated within the laboratory from genetically modified mice.
Authentication	Antibody staining (and RT-qPCR) for cell identity was performed prior to experimentation.
Mycoplasma contamination	All cultures were primary cultures that were used at early passage. They were not tested for mycoplasm contamination.
Commonly misidentified lines (See ICLAC register)	None of the cell lines used are listed in the ICLAC database

Animals and other organisms

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

Laboratory animals	P301S (MAPT) PS19 mice were purchased from The Jackson Laboratory (stock #008169) and bred to C57BL/6 for three generations. C57BL/6 ATTAC transgenic mice are as described {Baker et al., Nature 2016;Baker et al., Nature 2011}. Male PS19 mice were bred to ATTAC females to generate cohorts of ATTAC and PS19;ATTAC mice. All mice were on a pure C57BL/6 genetic background. Age range included postnatal day 1-3 for mixed glial cultures; 3, 4, 6, 8, 10, and 12 months ± 2 weeks of age for all in vivo experiments.
Wild animals	No wild animals were used in this study.
Field-collected samples	No field-collected samples were used in this study.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	All information is as described in the methods section.
Instrument	FACSAria IIu SORP (BD Bioscience)
Software	FACSDiva 8.0.1
Cell population abundance	The relative populations of cells were as follows (on average) from the 'live cells': Astrocytes (~27%), microglia (~14%), oligodendrocytes (~7%) and Cd56+ (~15%). Cell populations were verified with RT-qPCR for cell lineage markers.
Gating strategy	This information can be found in Extended Data Fig. 4. Additional information can be provided if necessary.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.