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Corresponding author(s): Melanie Meyer-Luehmann, Christian Haass

Reporting Summary

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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	Confocal images were acquired using a LSM 710 Confocal microscope (Zeiss) and the ZEN 2011 software package (black edition, Zeiss). Stacks were 3D reconstructed using IMARIS 8 software.
Data analysis	FIJI (ImageJ) was used for all immunohistochemical analyses. Excel 2011 (Microsoft v14.7.7) was used to calculate the averages of each repeated experiment. Graph Pad (Prism v7.0) was used to build graphs and perform statistical analyses presented throughout the manuscript. All PET analyses were performed by PMOD (v3.4, PMOD technologies, Basel, Switzerland). Sequences for genotyping of AD cases were aligned to the TREM2 reference sequence (UCSC genome browser, assembly GRCh38/hg38; chr6:41,158,506-41,163,186) and variants called manually by two investigators using the CLC Main Workbench Software (Qiagen). Mass-spectrometry analysis and label free protein quantification were performed with the Spectronaut software (v11.0.15038.4.29119, Biognosys) and Maxquant (v1.5.5.1).

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

The data that support the findings of this study are available from the corresponding author upon request.

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	Although no power calculation was performed prior to study design, sample size was determined based on experience from previous findings (Meyer-Luehmann et al. Science 2006) including the success rate of intrahippocampal injections for amyloid seeding. Sample sizes for PET study was based on Brendel et al. 2017, Front Aging Neurosci, and Grathwohl et al. 2009 Nat Neurosci for microglia-depletion experiments. Sample size for human cases were based on availability. For micro-PET experiments, we aimed to include 8 mice per group to account for drop outs. A power of 0.8 at an alpha < 0.05 was estimated by N=6. All number of mice and AD cases analyzed are reported in the respective sections (i.e. Figure Legends, Online methods).
Data exclusions	Data exclusion criteria were pre-established before starting the seeding experiments such that data were excluded if intrahippocampal injections for amyloid seeding were unsuccessful. The number of mice per genotype were excluded as follows: APPPS1/Trem2+/+=4; APPPS1/Trem2-/-=3 and APPPS1/Trem2p.T66M=3. One of the control AD cases without TREM2 coding variant was diagnosed with Hepatitis and therefore excluded from experiments involving frozen brains.
Replication	For all IF, each staining was performed on at least 3 sections per mouse with 3 technical replicates. For quantification of IF images, around 10 images analyzed per animal. Quantification for mouse tissue was excluded if tissue folds were present or the quality of the staining was poor. Experiments on human samples were repeated at least twice. Moreover, we controlled for artifacts resulting from long formaldehyde fixation period by staining freshly fixed frozen tissue and comparing different antigen retrieval methods. Samples were measured in duplicates for amyloid beta ELISA. The key findings on Trem2 dependent ApoE loading of amyloid plaques was repeated independently in the labs of Oleg Butovsky and David Holtzman. Both came to the same conclusion. All attempts of replications were successful and each experiment was reproduced with similar results. Reproducibility has been either indicated in the Figure Legends, or shown as a quantification.
Randomization	For all animal experiments, mice were allocated randomly after genotyping. Mice of different genotype were allocated randomly to PET experiments (scan number and slot) and with blinded identity to the experimenter (chipping system). No randomization procedure was performed for selecting patient material as case inclusion was largely based on availability.
Blinding	S.P. was not blinded during the intrahippocampal injection experiments, however all immunohistochemical analysis was performed blinded. Immunohistochemical staining of human postmortem tissue was performed blinded and analysis of sections done by S.P. and T.A. For microglia counts, slides were imaged and saved with random numbers to identify them. Images were then quantified and unblinded to perform group statistics.

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

Antibodies

Antibodies used

IBA1 (1:1000, Thermo Fisher Scientific, catalog number #PA5-27436, RRID: AB_2544912); IBA1 (1:500 IF or 1:1000 IHC, Wako, catalog number #019-19741 RRID: AB_839504); IBA1 (1:500, Abcam, catalog number ab5076, RRID: AB_2224402); Trem2 (1:50, R&D systems, catalog number AF1729, RRID:AB_354956); GFAP (1:1000, Thermo Fisher Scientific, catalog number #PA5-18598, RRID:AB_10984384); GFAP (1:3000, Dako, catalog number #N1506, RRID:AB_10013482); TUJ1 (1:1000, BioLegend, catalog number #MMS-435P, RRID:AB_2313773; CNPase (1:1000, clone 11-5B, Abcam, catalog number #ab6319, RRID:AB_2082593); Aβ1-16 (1:300, clone 6E10, BioLegend catalog number #803013, RRID:AB_2564765); Aβ17-24 (1:1000 IF or 1:4000 IHC, clone 4G8, BioLegend, catalog number #800703, RRID:AB_662812); Aβ1-40 (1:2000, clone 3552 In-house (Page et al., 2010 J Biol Chem)); CD68 (1:100, clone FA-11, Bio-Rad/Serotec, catalog number #MCA1957T, RRID:AB_2074849); Murine ApoE (1:300IF or 1:700 WB, clone HJ6.3/b, Holtzman lab (Kim et al., 2012 JEM)); Human ApoE (1:3000 IHC or 1:700 WB, clone HJ15.7, Holtzman lab (Liao et al., 2015 Acta Neuropathol Comm)). For more information, please refer to supplementary table 1.

Validation

IBA1 (AB_2544912, AB_839504 and AB_2224402), Trem2 (AB_354956), GFAP (AB_10984384), GFAP (AB_10013482), TUJ1 (AB_2313773), CNPase (AB_2082593), Aβ1-16 (AB_2564765), Aβ17-24 (AB_662812), CD68 (AB_2074849) are verified for immunostaining and immunoblotting in mouse and human on the company websites.

Trem2 (AB_354956) was verified for immunostainings by Jay et al., 2015 JEM and Yuan et al., 2016 Neuron. Aβ1-40 (clone 3552) was validated in Page et al,. 2010 J Biol Chem as well as in McCarter et al., 2013 Acta Neuropathol, Bachhuber et al., 2015 Nature Medicine and Ziegler-Waldkirch et al., 2018 EMBO J for immunostainings in mice.
Murine ApoE (clone HJ6.3/b) was previously validated and published by the Holtzman lab (Kim et al., 2012 JEM) for mouse tissue and (clone HJ15.7) for human tissue (Liao et al., 2015 Acta Neuropathol Comm).

Specificity of Trem2 and ApoE antibodies were further tested and validated by using samples from the appropriate knock-out mouse line. Specificity of 3552 amyloid beta antibody was also tested on non-transgenic C57BL6 mouse tissue.

Animals and other organisms

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

Laboratory animals

Seeding experiments:
4 months old male mus musculus APPPS1 (Thy1-APP695KM670/671NL; Thy-1PS1L166P) and age matched C57BL6 littermate controls were used. APPPS1 mice were crossed to TREM2-/- mice and maintained on a C57BL6J background. Additionally, APPPS1 were crossed to achieve homozygous TREM2 p.T66M knock-in mice (Kleinberger et al 2016, EMBO Journal), which were maintained on a mixed genetic background (N1 backcross to C57BL/6N). The TREM2 p.T66M mice were compared to APPPS1/TREM2 wild-type mice from the same background for all experiments.

Micro-PET experiments:
3, 6 and 12 months old female APPPS1/TREM2+/+ and age matched APPPS1/TREM2-/- were used. Additionally age, gender and genotype matched C57BL6 controls were also used.

Microglia isolation experiments:
Microglia were isolated from 3, 6 and 12 months old APPPS1 and age matched C57BL6 controls. Additionally, ApoE protein expression was performed on 12months old APPPS1/TREM2-/- mice with age matched APPPS1 controls. Both males and females were used for these experiments.

Microglia depletion experiments:
4 months old male APPPS1 mice crossed to HSTK expressing mice and treated with ganciclovir for two weeks for microglia depletion (Grathwohl et al. 2009, Nature Neuroscience). Additionally age and gender matched APPPS1 mice were used as controls.

Wild animals

No wild animals were used in this study.

Field-collected samples

No field-collected samples were used in this study.

Human research participants

Policy information about studies involving human research participants

Population characteristics	No living patients participated in this study. The patient characteristics for the postmortem samples included in this study are detailed in Online Methods and Supplementary Table 2. Case #1, Brain bank Munich, Clinical diagnosis: Dementia, not specified, 86 years old, Male, Post mortem delay 16-40 days, Braak & Braak AD stage 5, TREM2 variant p.R62H, ApoE E3/E3, Thal Phase 4, CERAD C, NIA classification A3 B3 C3 Case #2 Brain bank Munich, Clinical diagnosis: Dementia, not specified, 81 years old, Female, Post mortem delay information not available, Braak & Braak AD stage 5, TREM2 variant p.R62H, ApoE E3/E3, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #3, Brain Bank Munich, Diagnosis: Dementia with rapid progression, 75 years old, Male, Post mortem delay 24 days, Braak and Braak AD stage 6, TREM2 variant p.R62H, ApoE E3/E4, Thal Phase 5, CERAD C, NIA classifiation A3 B3 C3 Case #4, Brain Bank Munich, Diagnosis: Dementia Alzheimer type, 78 years old, Female, Post mortem delay 21 days, Braak and Braak AD stage 6, TREM2 variant p.R62H, ApoE E4/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #5, Brain Bank Munich, Diagnosis: Dementia frontotemporal, 77 years old, Male, Post mortem delay 26 days, Braak and Braak AD stage 5, TREM2 variant p.R62C, ApoE E3/E3, Thal Phase 4, CERAD C, NIA classification A3 B3 C3 Case #6, Brain Bank Munich, Diagnosis: Dementia frontotemporal, 78 years old, Male, Post mortem delay 5 days, Braak and Braak AD stage 5, TREM2 variant p.D87N, ApoE E3/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #7, Brain Bank UCL, Diagnosis: Pick's Disease, 71 years old, Male, Post mortem delay 40 days, Braak and Braak AD stage 6, TREM2 variant p.D87N, ApoE E3/E4, Thal Phase 5, CERAD C, NIA classficiation A3 B3 C3 Case #8, Brain Bank UCL, Diagnosis: Probable cortico-basal degeneration, 64 years old, Male, Post mortem delay 36 days, Braak and Braak AD stage 6, TREM2 variant p.R47H, ApoE E3/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #9, Brain Bank UCL, Diagnosis: AD, 66 years old, Female, Post mortem delay 51 days, Braak and Braak AD stage 6, TREM2 variant p.R47H, ApoE E4/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #10, Brain Bank Munich, Diagnosis: Dementia, Alzheimer type familial, 62 years old, Female, Post mortem delay 132 days, Braak and Braak AD stage 6, TREM2 variant None, ApoE E3/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #11, Brain Bank Munich, Diagnosis: Moderate dementia, probable Alzheimer type, 82 years old, Male, Post mortem delay 15 days, Braak and Braak AD stage 6, TREM2 variant None, ApoE E3/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #12, Brain Bank Munich, Diagnosis: Dementia Alzheimer type, 93 years old, Female, Post mortem delay information not available, Braak and Braak stage 5, TREM2 variant None, ApoE E4/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #13, Brain Bank UCL, Diagnosis: Young onset AD, 64 years old, Female, Post mortem delay 76 days, Braak and Braak AD stage 6, TREM2 variant None, ApoE E3/E3, Thal Phase 5, CERAD C, NIA classification A3 B3 C3 Case #14, Brain Bank UCL, Diagnosis: AD (Logopenic Asphasia), 62 years old, Male, Post mortem delay 34 days, Braak and Braak AD stage 6, TREM2 variant None, ApoE E3/E4, Thal Phase 5, CERAD C, NIA classification A3 B3 C3
Recruitment	All patient material was obtained from people who had enrolled in the brain donation program while still alive. All material collection procedures were approved by the ethical committee. Therefore no investigator bias was present that could impact results.