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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 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-maze software (Stoelting Co.) BD Attovision (BD bio-science) Imaris, version 7.1.1, Bitplane ImageJ - (National Institutes of Health) NIS Elements software (Nikon Instruments Inc.) Illumina local run manager (Illumina)
Data analysis	NIS Elements software (Nikon Instruments Inc.) GraphPad Prism (v8.3.1) MATLAB (Math Works) Subread/featureCounts (v1.5.3; https://sourceforge.net/projects/subread/files/subread-1.5.3/) Rsubread (v1.34.2; https://bioconductor.org/packages/release/bioc/html/Rsubread.html) edgeR (v3.26.5; https://bioconductor.org/packages/release/bioc/html/edgeR.html) Database for Annotation, Visualization and Integrated Discovery (DAVID v6.8, https://david.ncifcrf.gov) Cell Ranger 3.0.1 pipeline (https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger) Seurat v3.0.2 (https://satijalab.org/seurat/)

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 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 RNA-seq expression data has been deposited in the GEO database under the accession number: To Be Determined.

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	Sample size was determined using G* power
Data exclusions	No data was excluded
Replication	For shotgun lipidomics on ACM 2 cultures were analyzed in duplicate, all microglia in vitro aB uptake assays were run as a replicate of three.
Randomization	All samples were randomized into experimental groups, with each experimental group represented in a batch
Blinding	Researchers were blinded to excremental groups at all stages of the study

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	Anti-IBA1 antibody Wako Cat No. 019-19741, RRID:AB_839504 Normal Donkey Serum Jackson Lab Cat No.017-000-121, RRID:AB_2337258 Donkey anti-rabbit Alexa 594 Invitrogen Cat No. R37119, RRID:AB_2556547 F4/80 Abcam Cat No. ab6640 Human APOE Meridian Life Sciences Cat No. K74180B anti-mouse/human CD11b (M1/70) BioLegend Cat No. 101218, RRID:AB_389327 smFISH probe: Mm-Tmem119 Advanced Cell Diagnostics Cat No. 472901 smFISH probe: Mm-Adgre1 Advanced Cell Diagnostics Cat No. 460658
Validation	All antibodies are commercially available and have been validated by each respective company

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Primary astrocytes were established from one-day-old E3, E4, E3/ABCA1het and E4/ABCA1het targeted replacement pups. Primary microglial culture and Aβ uptake assay were performed using WT, E3, E4, E3/Trem2ko and E4/Trem2ko pups (1-3 days old)
Authentication	The cell lines were authenticated using genotyping
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	Not applicable

Animals and other organisms

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

Laboratory animals	Wild-type C57BL/6J (WT; JAX) human APOE3 and APOE4 targeted replacement mice (E3 & E4; Taconic) Trem2em2ADiuj/J mice (Trem2ko; JAX) 129P2(Cg)-Cx3cr1tm1Litt/J (Cx3cr1GFP; JAX). Human APOE3 and APOE4 targeted replacement mice were bred to Abca1tm1Jdm/J mice (Abca1ko; JAX) to generate APOE3/Abca1het and APOE4/Abca1het (E3het & E4het). Likewise, human APOE3 and APOE4 targeted replacement mice were bred to Trem2em2ADiuj/J mice (Trem2ko; JAX) to generate APOE3/Trem2ko and APOE4/Trem2ko (E3/Trem2ko & E4/Trem2ko).
Wild animals	The study did not involve wild animals
Field-collected samples	The study did not involve samples collected in the feild
Ethics oversight	All animal experiments were performed in accordance with the NIH Guide for Care and Use of Animals and approved by the University of Pittsburgh Institutional Animal Care and Use Committee.

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	Average PMI = 4.1 Average age at death = 80.35 average braak stage = 6 Percentage female = 42.86 Age and Postmortem intervals (PMI) matching was confirmed by t test.
Recruitment	Human post-mortem AD samples were provided by the University of Pittsburgh Alzheimer's Disease Research Center (ADRC) brain bank and the Sanders-Brown Center on Aging at the University of Kentucky.
Ethics oversight	University of Pittsburgh Alzheimer's Disease Research Center (ADRC)

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

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	For the Cx3cr1GFP mice infused with HiLyte™ Fluor 555-labeled Aβ, microglia were isolated utilizing FACS. After removing the cerebellum, subcortical area and olfactory bulbs, cortical tissue within 1 mm of either side of the infusion site was processed into a single-cell suspension using the Neural Tissue Dissociation kit followed by the Myelin Removal Beads II (Miltenyi Biotec)

	as described above. For WT and TREM2ko mice, after the myelin removal steps the pellet were resuspended with 100 µl of PBS and the microglia cells were labeled with 5 µl of anti-mouse/human CD11b antibody (clone M1/70) conjugated with Alexa Fluor 647 (BioLegend) for 20 min on ice. All cells were then washed and prepared with 1 mL of PBS + 0.5% BSA for FACS sorting.
Instrument	bio-contained BD FACSAria
Software	BD Attovision
Cell population abundance	The microglia cell population of interest (total microglia) accounted on average for 8.2% of the cells analyzed.
Gating strategy	live cells were separated from the debris according to their forward scatter and side scatter properties and a second gate was used on individual cells only. The GFP fluorescence was detected with a 525 nm filter (488 nm laser) for the microglia isolated from the Cx3cr1GFP mice, the CD11b/APC fluorescence was collected with a 668 nm filter (647 nm laser) for the WT and TREM2ko mice and the 555-labeled Aβ fluorescence was detected with a 613 nm filter (555 nm laser). Boundaries were defined using negative controls.

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