

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 (<i>n</i>) 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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	FreezeFrame (Actimetrics),EthoVision XT 15 (Noldus) RRID:SCR_004074, Leica SP8 confocal laser microscope and LAS software were used to capture images,
Data analysis	Chopra Lab in-house software, Lipidome Gene Enrichment Reactions (LIGER), Fiji software, CLAW https://github.com/chopralab/CLAW , LipidSig 2.0 https://lipidsig.bioinfomics.org/ , R Project for Statistical Computing RRID:SCR_001905, Prism 9, Image-J software. Imaris for Neuroscientists (version 10.2, released June 26 2024; Oxford Instruments, Zurich, Switzerland)(free trial version), Ilastik (version 1.4.1.post1, released May 31 2025; University of Heidelberg and MPI-CBG, Germany), AlphaFold 3, PyMOL (Schrödinger, LLC), BioRender. Lab, C. (2026) https://BioRender.com/skekqpw

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](#)

Code for all the data analysis is publicly available on: <https://github.com/chopralab/PLA2G2F-Lipidomics>.
RNA sequencing data is accessible through GEO: GSE261906

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

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

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	Based on prior work and pilot experiments using same strain of mice
Data exclusions	No data were excluded from the study
Replication	Multiple cohorts of mice tested across different ages for same manipulation yielded similar outcomes. We adhered to accepted standards for rigorous study design and reporting to maximize the reproducibility and translational potential of our findings as described by Landis, S.C et al., 2012 and in Arrive Guidelines by Kilkenny, C., et al., 2010.
Randomization	Animals were randomized for behavioral testing (different treatment groups). Age-matched mice were used for this study and cagemates were randomly assigned to groups during virus injection
Blinding	Investigators were blinded to treatment groups. treatment conditions throughout data collection, scoring, and analyses. Multiple investigators scored same dataset.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used

Rabbit anti-Iba1 1:500 WAKO 019-19741, RRID:AB_839504
 Rabbit anti-GFAP, 1:500 DAKO Z0334, RRID:AB_10013382
 Chicken anti-GFP, 1:500 Aves 1020, RRID:AB_10000240
 Rat anti-CD68 1:200 Biorad MCA 1957, RRID:AB_322219
 Goat anti-PV antibody, 1:5000 Swant PVG213; RRID: AB_2721207
 Rabbit anti-RFP antibody, 1:200 Rockland 600-401-379; RRID: AB_2209751
 Mouse 6E10 anti-Abeta 1-16, 1:500 Biolegend 80300, RRID:AB_2565329
 Guinea Pig anti-CFOS 1:3000 Synaptic Systems 226308, RRID:AB_2905595

Validation

All antibodies used are commercially available and were selected because they were previously validated for mouse reactivity and for immunohistochemistry use. These antibodies have been widely used in peer reviewed publications

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

iPSC derived neuronal organoids and iMGLs. 293FT Cell Line from ThermoFisher Scientific (catalog number R70007) was used for lentiviruses production. The ApoE3 iPSC line was generated from the Coriell Institute's fibroblast line derived from a healthy individual (age 75 years, female; #AG09173) by Dr. Yankner's Laboratory at Harvard Medical School.

Authentication

Victor, M.B., Leary, N., Luna, X., Meharena, H.S., Scannail, A.N., Bozzelli, P.L., Samaan, G., Murdock, M.H., von Maydell, D., Effenberger, A.H., et al. (2022). Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. Cell Stem Cell 29, 1197-1212 e1198. 10.1016/j.stem.2022.07.005.

Successful lentiviral packaging reaction was assessed using Lenti-X GoStick titer test (Takara 631281). Lentiviruses were injected in mice and expression of the reporter was assessed by IHC. iPSCs were reprogrammed in the Tsai Lab, followed by karyotyping and pluripotency validation in house

Mycoplasma contamination

Negative for mycoplasma. Cell lines are routinely tested for mycoplasma and deemed free of contamination prior to study

Commonly misidentified lines
(See [ICLAC](#) register)

None were included in this study

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals

Male C57Bl/6J, adult, middle-aged and aged mice (3,6,12,16,18 months) were ordered from National Institute of Aging (NIA). Pla2g2f/f mice were generated previously and obtained from Dr. Makoto Murakami. CamKIIα-Cre-ERT2 mice were previously generated and obtained from Dr. Richard L. Huganir.

Wild animals

This study did not involve wild animals

Reporting on sex

Male and female mice were used. Aging cKO mice cohorts involved male and female mice.

Field-collected samples

NA

Ethics oversight

All mice were group housed and experiments were conducted in accordance with procedures approved by the Institutional Animal Care and Use Committees at the Massachusetts General Hospital and NIH guidelines (IACUC 2011N000084).

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