

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	1. ZEN black (version 2.3, Carl Zeiss Microscopy GmbH) connected to an inverted Zeiss LSM microscope - live/fixed imaging. 2. CellIR Software (Olympus) on an Olympus IX81 with an UAPO/340 40x oil objective (1.35 NA) - calcium imaging. 3. Read Sector Imager 6000 (Meso Scale Discovery) - Western blotting. 4. ANY-maze tracking software (Stölting) - mouse behavior tests.
Data analysis	1. Image J Software (Schindelin et al., 2012; Schneider et al., 2012) for immunofluorescent image analysis. 2. RADIUS 2.0 (Build 14402, Emsis) software for EM analysis. 3. Prism GraphPad (v9.2.0; La Jolla, CA, USA) for statistical analysis and visual representation. 4. Multi Channel Experimenter software (Multichannel Systems) for electrophysiology.

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](#)

The data generated and analysed in this study are included in this published article (and its supplementary information files). Source data are provided with this paper.

Human research participants

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

Reporting on sex and gender	Not applicable
Population characteristics	Not applicable
Recruitment	Not applicable
Ethics oversight	Not applicable

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	No statistical methods were used to predetermine the sample size; n-values were based on our previous studies (PMID: 34292306, PMID: 28134274, PMID: 27293189).
Data exclusions	Not applicable.
Replication	For all experiments, data are reported based on individual cells/mice or biological replicates pooled from multiple cells, e.g. lysates. Individual cell values were obtained from at least 3 independent dishes/coverslips unless stated otherwise. Western blots are representative of two or more replicates (as indicated in analysis graphs and the source data file). Statistical analysis was performed as from n=3.
Randomization	Not applicable. The samples were grouped based on their genotype or treatment condition. By keeping neuron cultures in the same growth and medium conditions, covariates were minimized.
Blinding	In this study, the investigators were not blinded during data collection and/or analysis.

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	Mouse anti-human Aβ (82e1, 10323, Tecan, 1:100 for IF, 1:500 for WB) Mouse anti- actin (A5441, Sigma Aldrich, 1:10 000 for WB) Mouse anti-ankyrin-G coupled to FL550 (75-146-FL550, NeuroMab, 1:500) Mouse anti-GluR1 (MA5-27694, Invitrogen, 1:500 for IF, 1:1000 for WB), Mouse anti-nicastrin (9C3, home-made, 1:8000 for WB) Mouse anti- synaptobrevin2 (104 211, Synaptic Systems, 1:500 for IF) Rabbit anti-human Aβ fibrils (AB2287, Sigma Aldrich, 1:200 for IF) Rabbit anti-APP (Y188, Ab32136, Abcam, 1:500 for IF) Rabbit anti-APP (B63.3, home-made, 1:10 000 for WB) Rabbit anti-EEA1 (07-1820, Sigma Aldrich, 1:250 for IF) Rabbit anti-presenilin 1 (B19, home-made, 1:20 000 for WB) Rabbit anti-presenilin 2 (ab51249, abcam, 1:500 for IF, 1:10 000 for WB) Rat anti-Lamp1 (1D4B, sc19992 Santa Cruz, 1:200 for IF, 1:1000 for WB) Chicken anti-Map2 (PA1-10005, Thermo Fisher, 1:5000 for IF) Goat anti-VPS35 (ab10099, Abcam, 1:200 for IF) PSD 95 nanobody-647 (N3702-AF647-L, Synaptic Systems, 1: 500 for IF)
Validation	Antibodies were chosen from previous publications and/or validation by the manufacturers for their intended use. Where possible, we examined the antibodies' specificity, checking the target's known cellular localization, test their known responsiveness to stimuli and/or used knockdown or knockout cell lines.

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	Mice carrying a FAD Psen2 mutation N141I were generated using CRISPR-Cas9 technology to target exon 6 of the mouse Psen2 gene. Psen2KO and APP NL-G-F (also in C57BL/6J background) were kindly provided by Bart de Strooper and Takaomi Saido. Respective ages are indicated in the figures/results.
Wild animals	No wild animals were used in this study.
Reporting on sex	Only female mice were used for experiments, while neuronal cultures were generated from all embryos without checking for gender. The research findings as such do not apply to only one sex or gender.
Field-collected samples	The study does not include field-collected samples.
Ethics oversight	All experiments were approved by the KU Leuven ethical committee (ECDs: 174/2017, 173/2022, Creation Annaert Willem/2020).

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