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# Life Sciences Reporting Summary

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For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

## Experimental design

1. Sample size

Describe how sample size was determined.

The sample size (n) for each experimental group is described in each figure legend. For mouse experiments and for motility, fitness and death scoring experiments in C. elegans, sample size was estimated based on the known variability of the assays.

2. Data exclusions

Describe any data exclusions.

Animals that showed signs of severity, predefined by the animal authorizations were euthanized. These animals, together with those who died spontaneously during the experiments, were excluded from the calculations. These criteria were established before starting the experiments.

3. Replication

Describe whether the experimental findings were reliably reproduced.

all attempts at replication were reproducible

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Mice were housed by groups of 2 to 5 animals per cage and randomized to 7-8 animals per experimental group according to their body weight.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

All experiments were done non-blinded

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

| n/a | Confirmed |
|---|---|
| ☐ | ☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.) |
| ☐ | ☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ A statement indicating how many times each experiment was replicated |
| ☐ | ☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section) |
| ☐ | ☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons |
| ☐ | ☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted |
| ☐ | ☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range) |
| ☐ | ☒ Clearly defined error bars |

*See the web collection on statistics for biologists for further resources and guidance.*

## Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.

GraphPad Prism 6 (GraphPad Software, Inc.) was used for all statistical analyses.
For the generation of correlation plots (Fig 1c and Extended Data Figure 1a,c), the R software package was used (https://www.r-project.org/). The GSEA software was used for GSEA analysis of expression datasets (http://software.broadinstitute.org/gsea/index.jsp) (Fig. 1 and Extended Data Fig. 1).
For fear conditioning assays, the MED PC-IV software (Med Associates, USA) was used to control the presentation of the stimuli (tone and shock).
Western blots were imaged using the c300 imaging system (Azure Biosystems).
Pixel intensity for blots and microscopy pictures was quantified by using ImageJ and Fiji softwares.
Mobility of worms: C. elegans movement analysis was performed as described, starting from day 1 of adulthood, using the Movement Tracker software.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

## Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

We generated novel C.elegans strains, which are listed here and in Extended Data Table 14, which are freely available upon request. There are no restrictions on the availability of the other materials used in the study.
Strains generated in this study:
CL2122 3x backcrossed in N2
AUW9
AUW10
AUW11
AUW12
AUW13

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

This is fully reported in the Extended Table 11. List of antibodies
Antibody Supplier Reference # Validation Species
HSP60 ,Enzo Life Science ADI-SPA-806 manufacturer Mouse
CLPP, Sigma WH0008192M1 manufacturer Mouse
GAPDH, (14C10) Cell Signaling 2118S manufacturer Mouse
LONP1, Sigma HPA002192 manufacturer Mouse
PINK1 ,Novus Biologicals BC100-494 manufacturer Mouse
LC3 A/B, Cell Signaling 4108S manufacturer Mouse
SDHB, Abcam ab110413 manufacturer Mouse
MTCO1, Abcam ab14705 manufacturer Mouse
SQSTM1, BD Transduction Laboratories 610497 manufacturer Mouse
Phospho SQSTM1, Cell signaling 95967 manufacturer Mouse
VDAC, Abcam ab14734 manufacturer Mouse
Ubiquitin, Enzo Life Science BML-PW8810-0100 manufacturer Mouse
β-amyloid,1-16 (6E10) ,BioLegend 803002 manufacturer Mouse, Human
β-amyloid,17-24 (4G8) ,BioLegend 800701 manufacturer Mouse, Human
anti-Oligomer (A11), Thermo Scientific AHB0052 manufacturer Mouse, Human
CLPP (2E1D9) ,ProteinTech 66271-1-Ig manufacturer Human
GAPDH (2D9) ,Origene TA802519 manufacturer Human
mtDnaJ (RS13) ,Cell Signaling 4775S manufacturer Human
Anti-Beta-Amyloid 1-42, Millipore AB5078P manufacturer Human
Actin Sigma A5441, manufacturer Human, mouse, worm
Tubulin Santa Cruz Sc-5286, manufacturer Human, mouse, worm
For immunofluoresce, the secondary antibody was coupled to the Alexa-488 fluorochrome (Thermo Scientific). For blotting, near-infrared-labeled goat anti-mouse IgG secondary antiserum or goat anti-mouse IgG incubation and Odyssey imaging , or Goat anti-mouse IgM-HRP (sc-2973) and Anti Rabbit HRP (jackson, 711-035-152) were used.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

The SH-SY5Y neuroblastoma cell line expressing the APP Swedish K670N/M671L double mutation (APPSwe) (ref 35) was a kind gift of Prof. Cedazo-Minguez (Karolinska Institute, Sweden).

b. Describe the method of cell line authentication used.

Cells were selected in 4 µg/mL Geneticin® Selective Antibiotic (G418 Sulfate, Sigma) and grown for three generations before experiments, and validated by immunostaining methods, as published by Prof. Cedazo-Minguez lab. In particular, we used antibodies against beta-amyloid peptides to confirm the expression of the APP mutant transgene. We also used qPCR to detect mRNA levels of the APP mutant transgene in the cell line, so we could confirm the identity of the cell ine

c. Report whether the cell lines were tested for mycoplasma contamination.

Cells were tested for mycoplasma and resulted negative to mycoplasma.

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.

no commonly misidentified cell lines were used

## Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

### 11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

3xTg AD mice, bearing human mutant APPswe, PS1M146V, and TauP301L transgenes18, and wild-type, hybrid 129/C57BL6 mouse littermates were transcardially perfused with saline at 6 and 9 months of age (n = 6/group) and brains from each group were hemisected. One hemisphere was immersion-fixed in 4% paraformaldehyde/0.1% glutaraldehyde for 24 hours and stored in cryoprotectant. From the other hemisphere, hippocampus, frontoparietal cortex, and cerebellum were rapidly dissected and snap-frozen.
APP/PSEN1 mice (Tg(APPswe,PSEN1dE9)85Dbo/Mmjax) were purchased from JAX. APP/PSEN1 mice were fed with pellets containing vehicle or NR (400 mg/kg/day) for 10 weeks, starting at the age of 4 months. The pellets were prepared by mixing powdered chow diet (2016S, Harlan Laboratories) with water or with NR dissolved in water. Pellets were dried under a laminar flow hood for 48 hours. Mice were housed by groups of 2 to 5 animals per cage and randomized to 7-8 animals per experimental group according to their body weight. No blinding was used during the experiment procedures. This information is available also on page 34 of the main text file.
The experiments with the 3xTg mice were authorized by the MSU Institutional Review Board and Institutional Animal Care and Use Committee. The experiments with APP/PSEN1 mice were authorized by the local animal experimentation committee of the Canton de Vaud under license 3207.

For C. elegans, a total of ≈3000 worms per condition, divided in 3 biological replicates, was recovered in M9 buffer from NGM plates and lysed in the TriPure RNA reagent for RNA analysis and western blotting.
C. elegans strains were cultured at 20°C on nematode growth media (NGM) agar plates seeded with E. coli strain OP50 unless stated otherwise. Strains used in this study were the wild-type Bristol N2, GMC101 [unc-54p::A-beta-1-42::unc-54 3'-UTR + mtl-2p::GFP]23, CL2122 [(pPD30.38) unc-54(vector) + (pCL26) mtl-2::GFP]59, CB4876 (clk-1(e2519)) and MQ1333 (nuo-6(qm200)). Strains were provided by the Caenorhabditis Genetics Center (University of Minnesota). The strain CL2122 was outcrossed 3 times in the N2 background, and subsequently used in the control experiments reported herein. AUW9 and AUW10: [GMC101 +epfEx6[atfs-1p::atfs-1]], and AUW11: [CL2122+epfEx7[atfs-1p::atfs-1]] overexpression strains, and AUW12: [GMC101+clk-1(e2519) III], AUW13: [GMC101 +nuo-6(qm200) I] were generated within this study.Compounds were added just before pouring the plates. For phenotyping experiments, parental F0 L4 worms were allowed to reach adulthood and lay eggs on the treatment plates. The deriving F1 worms were therefore exposed to compounds during the full life from eggs until death. For RNA analysis experiments, synchronized L1 worms were exposed to the compounds until harvest. To ensure a permanent exposure to the compound, plates were changed twice a week.

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Superior temporal cortex (Brodmann area 22) samples were obtained postmortem from participants in the Religious Orders Study who died with an antemortem clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI), or AD (n = 8/group) Extended Data Table 8). Neuropsychological and clinical examinations, as well as postmortem diagnostic evaluations, have been described elsewhere. Demographic, antemortem cognitive testing, and postmortem diagnostic variables were compared among the groups using the nonparametric Kruskal-Wallis Test with Bonferroni correction for multiple comparisons. Gender and apoE ε4 allele distribution were compared using Fisher's Exact Test with Bonferroni correction. This information is also reported on page 39 of the main text file, and in Extended Data Table 8.The experiments with postmortem human samples were authorized by the Michigan State University (MSU) Human Research Protection Program.

Human datasets for bioinformatics studies

For the in silico analysis of human brain expression datasets, we have used two sets of publicly available RNA-seq data: (1) from the Harvard Brain Tissue Resource Center (HBTRC), for human primary visual cortex (GN Accession: GN327) and human prefrontal cortex (GN Accession: GN328), and (2) from the Translational Genomics Research Institute, for the whole brain (GN Accession: GN314). These two datasets are publicly available on GeneNetwork (www.genenetwork.org).

GN327 and GN328 are two sets of publicly available RNA-seq data generated by the Harvard Brain Tissue Resource Center (HBTRC). The 803 participants in this dataset are composed of 388 Alzheimer's disease cases and 195 controls matched for age, gender, and post mortem interval (as well as 220 Huntington's disease cases). Three brain regions including the cerebellum, the visual cortex and the dorsolateral prefrontal cortex from the same individuals were profiled on a custom-made Agilent 44K microarray. Clinical outcomes available include age at onset, age at death, Braak scores and Regional brain enlargement/atrophy. In our study, we have analyzed the visual cortex (GN237) and the prefrontal cortex (GN238).

GN314 is a set generated by Translational Genomics Research Institute. This human brain expression data was obtained from patients with Alzheimer's disease and age-matched elderly control subjects. Samples were recovered from cortical regions of 14 normal elderly humans (10 males and 4 females) and from 33 AD cases (15 males and 18 females). 6 brain regions were analyzed with about 14 biological replicates per brain region. The brain regions are as the entorhinal, hippocampus, medial temporal gyrus, posterior cingulate, superior frontal gyrus and primary visual cortex. Mean age of cases and controls was 80 years. All samples were run on the Affymetrix U133 Plus 2.0 array.