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☐ Initial submission ☐ Revised version ☒ Final submission

# Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

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.

Sample sizes for both biochemical and behavioral experiments were determined based on calculations performed on empirical data and power analyses. The number of animals used for each experiment was appropriate to detect biochemical or behavioral differences with 80% power and alpha set at 0.05.

2. Data exclusions

Describe any data exclusions.

For experiments using AAV to transduce neurons and drive gene expression in the hippocampus, exclusion criteria were pre-established such that transduction was assessed in all mice by a person blinded to the genotype/treatment of the mice. Mice that did not exhibit expression in the hippocampus were excluded from analysis.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All attempts at replicating experiments presented in the manuscript have been successful.

4. Randomization

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

No specific method of randomization was used, but animals were semi-randomly assigned to experimental groups based on birth order after balancing for age, sex, and genotype.

5. Blinding

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

For all data collection/analyses, the experimenters were blinded to the genotype and treatment type of each mouse.

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. | Statistical analyses were performed using SPSS-23 (IBM) and Prism 7 (GraphPad). |

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. | AAV-CMV-mCalb1-IRES2-eGFP was synthesized for our use by Vector Biolabs (Philadelphia, PA), and is available for purchase from them upon request for custom synthesis. No other unique materials were used in this study. |

9. Antibodies

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

All antibodies were internally validated for use in each application listed via pilot experiments involving serial dilutions (in accordance with recommendations from suppliers). Data demonstrating signal-to-noise for antibodies are shown in the manuscript. The final dilution/concentration used for each antibody is:

Immunofluorescent immunohistochemistry:
rabbit anti-ΔFosB (1:100, Cell Signaling 9890; 1:1000, Cell Signaling D3S8R), mouse anti-calbindin (1:1000, Swant 300), mouse anti-NeuN (1:5000, Millipore MAB377), goat anti-cFos (1:300, Santa Cruz Biotechnology sc-52g), donkey anti-rabbit AMCA (1:200, Jackson ImmunoResearch 711-155-152), donkey anti-goat Cy3 (1:200, Jackson ImmunoResearch 705-165-147), donkey anti-mouse Alexa Fluor 594 (1:500, Life Technologies A-21203), donkey anti-rabbit Alexa Fluor 488 (1:500, Life Technologies A-21206)

Diaminobenzidine immunohistochemistry:
rabbit anti-ΔFosB (1:300, Cell Signaling 9890), rabbit anti-calbindin (1:15,000, Swant CB-38A), rabbit anti-JunD (1:1000, Santa Cruz Biotechnology sc-74), biotinylated goat anti-rabbit (1:200, Vector BA-1000)

In situ hybridization:
alkaline phosphatase-conjugated sheep anti-digoxigenin antibody (1:5000, Roche 11333089001)

Chromatin immunoprecipitation:
rabbit anti-ΔFosB (2 µg, Cell Signaling 9890 and D3S8R), rabbit anti-H3K9+K14+K18+K23+K27ac (2 µg, Abcam ab47915), rabbit anti-H4K5+K8+K12+K16ac (2 µg, Millipore 06-866), rabbit anti-H3K9me2 (2 µg, Abcam ab1220), rabbit anti-H3K9me3 (2 µg, Millipore 07-442), rabbit anti-H4K20me3 (2 µg, Millipore 07-463), and normal rabbit IgG (2 µg, Millipore 12-370)

10. Eukaryotic cell lines

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

No eukaryotic cell lines were used.

b. Describe the method of cell line authentication used.

n/a

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

n/a

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.

n/a

## 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.

Heterozygous amyloid precursor protein (APP) transgenic mice expressing human APP carrying the Swedish (K670N, M671L) and Indiana (V717F) familial AD mutations (hAPP770 numbering) driven by the platelet-derived growth factor (PDGF) β chain promoter (Line J20)16 were used in this study. The line was crossed for >10 generations onto a C57BL/6 background, and heterozygosity was maintained by breeding with wild-type C57BL/6 mice from The Jackson Laboratory (Bar Harbor, ME). Male and female mice from this line were used for experiments, and were evaluated at 2-4 months of age. At this age, many APP mice exhibit both recurrent seizures and cognitive deficits, but no plaque deposits. Age- and sex-matched nontransgenic wild-type animals from the same line were used as controls.

Policy information about studies involving human research participants

## 12. Description of human research participants

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

Postmortem dentate gyrus samples from patients diagnosed with mild cognitive impairment (MCI) or Alzheimer's disease (AD) were obtained from the Alzheimer's Disease Research Center at the University of California San Diego (San Diego, CA). Patients had been diagnosed based on combination of Mini-Mental State Exam performance and Braak staging. Both sexes were included, with ages ranging from 56-94.

Dentate gyrus samples from temporal lobe epilepsy patients were obtained and used with informed consent under IRB protocol H-10255, using epilepsy surgery resection specimens derived from adult patients treated at Baylor College of Medicine (Houston, TX). Both sexes were included, with ages ranging from 32-60.