

Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
- ☐ ☒ An indication of 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 statistics 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
- ☐ ☒ Clearly defined error bars
State explicitly what error bars represent (e.g. SD, SE, CI)

Our web collection on [statistics for biologists](#) may be useful.

Software and code

Policy information about [availability of computer code](#)

Data collection

ANY-Maze 2, Noldus Ethovision XT, Zeiss Axiovision 4.8, pClamp 10 (Molecular Devices), Microsoft Office 2008 for Mac, Li-cor Image Studio 3.0, SpectaMax Softmax Pro 6, Applied Biosystems 7500 Real-Time PCR software.

Data analysis

ANY-Maze 2, Noldus Ethovision XT, Zeiss Axiovision 4.8, pClamp 10 (Molecular Devices), Microsoft Office 2008 for Mac, GraphPad Prism 6, Fiji 3.0, Applied Biosystems 7500 Real-Time PCR software, Qiagen RT2 Data Profiler.

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/reviewers upon request. 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

Mass spectrometry raw data (Figure 1; Extended Data Figure 1) and full blots (Figure 2; Extended Data Figures 3,4 and 10) are available as source data files

accompanying this paper. Additional data that support the findings of this study are available from the corresponding author upon reasonable request. Requests of datasets obtained from human research will be subject to additional reviews steps by the Institutional Review Board who has granted permit for a particular research. Please contact the corresponding authors for additional information.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size for each experiment was estimated by performing pilot studies and by previous experience with different experiments. The rationale was to obtain robust measurements according to the type of experiment, taking variability into consideration. For some experiments, power analyses were performed prior to the start.
Data exclusions	In NOR tests, animals were excluded from the analyses if they had less than 8s of total exploration in the training or the testing phase. This was pre-established. No other exclusion criteria was employed in animal studies.
Replication	Studies involved replication of experimental findings whenever possible. Behavioral tests were performed in different cohorts of animals. Culture experiments were performed independent cultures. We did not have failed replications in the experiments presented in this study.
Randomization	No algorithm or software was used to randomize animal subjects. Animals were randomly assigned to groups by trained researchers performing each experiment.
Blinding	Experiments involving image analyses, electrophysiology, and behavioral tests in mice were performed in blinded fashion.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Antibodies

Antibodies used	anti-ATF4 antibody (Sigma, #WH0000468M1, monoclonal, clone 2B3, 1:500), anti-eIF2 α -P (phosphoS51) (Enzo Life Sciences, #BML-SA405-100, polyclonal 1:500), anti-eIF2 α (total) (Enzo Life Sciences, #ADI-KAP-CP130, polyclonal, 1:400), anti-puromycin (12D10) (EMD Millipore, #MABE343, monoclonal, clone 12D10, 1:5000), anti-FNDC5 (Abcam, #ab131390, polyclonal, 1:500), anti- β -actin (Abcam, #ab8226, monoclonal, clone 8226, 1:20000), anti-GAPDH (Abcam, #ab9485, polyclonal, 1:2000), Tuj1 (R&D, #MAB1195, monoclonal, clone Tuj1), anti-BDNF (Santa Cruz, #sc546, polyclonal, 1:500).
Validation	Antibodies were used according to manufacturer's instructions. Antibody validation for the species/application can be found at the suppliers' webpage. Additional validation for the anti-FNDC5 antibody by immunoblotting and mass spectrometry is present in Extended Data Figure 1 and in Source Data.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals	This work involved use of 3-month old male WT C57BL/6 or Swiss mice, as reported in each figure. In experiments involving transgenic APP/PS1 mice (on a C57BL/6 background), both males and females were used, and were aged 6-13 month-old.
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Wild animals

This study did not involve wild animals.

Field-collected samples

This study did not involve samples collected from field research.

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics

Healthy cortical tissue was obtained from patients with drug-resistant temporal lobe epilepsy subjected to surgical interventions for removal of epileptic foci. Donors were two males (aged 37 and 49 year-old) and three female (aged 18, 39 and 66 year-old). AD tissue was from symptomatic individuals with clinical and pathological features described in Supplementary Table 1. All subjects were categorized by MMSE as control (26-30), early AD (20-25), and late AD (13-17). Sample groups were separated so as to clearly define differences in content of proteins of interest and MMSE score. Cerebrospinal fluid (CSF) or plasma from control and AD patients was collected after extensive neuropsychological investigation supervised by a board-certified psychiatrist, as described. The study cohort included males and females. Age (mean $\pm$ SD), in years, was distributed as follows: Controls (67.5 ± 4.9), MCI (71.5 ± 5.8), AD (72.5 ± 8.1), and LBD (71.6 ± 7.0).

Recruitment

For the CSF study, patients were recruited by the IDOR memory clinic after subjective memory complaints, as reported in Methods. For the ex vivo human cortical slices, patients were subjected to lobectomy after extensive clinical examination and explicit diagnosis of refractory epilepsy by board-certified neurologists at the University Hospital. Brain tissue would be otherwise discarded. All studies are in compliance with local and international regulations, and were approved by competent ethics committees. In all cases, diagnosis was defined by board-certified neurology committees, and there is no anticipated potential bias during selection.