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Supplementary Tables: 0

Supplementary Videos: 0

Reporting Checklist for Nature Neuroscience

This checklist is used to ensure good reporting standards and to improve the reproducibility of published results. For more information, please read Reporting Life Sciences Research.

Please note that in the event of publication, it is mandatory that authors include all relevant methodological and statistical information in the manuscript.

Statistics reporting, by figure

- Please specify the following information for each panel reporting quantitative data, and where each item is reported (section, e.g. Results, & paragraph number).
- Each figure legend should ideally contain an exact sample size (n) for each experimental group/condition, where n is an exact number and not a range, a clear definition of how n is defined (for example x cells from x slices from x animals from x litters, collected over x days), a description of the statistical test used, the results of the tests, any descriptive statistics and clearly defined error bars if applicable.
- For any experiments using custom statistics, please indicate the test used and stats obtained for each experiment.
- Each figure legend should include a statement of how many times the experiment shown was replicated in the lab; the details of sample collection should be sufficiently clear so that the replicability of the experiment is obvious to the reader.
- For experiments reported in the text but not in the figures, please use the paragraph number instead of the figure number.

Note: Mean and standard deviation are not appropriate on small samples, and plotting independent data points is usually more informative. When technical replicates are reported, error and significance measures reflect the experimental variability and not the variability of the biological process; it is misleading not to state this clearly.

		TEST USED		n			DESCRIPTIVE STATS (AVERAGE, VARIANCE)		P VALUE		DEGREES OF FREEDOM & F/t/z/R/ETC VALUE	
	FIGURE NUMBER	WHICH TEST?	SECTION & PARAGRAPH #	EXACT VALUE	DEFINED?	SECTION & PARAGRAPH #	REPORTED?	SECTION & PARAGRAPH #	EXACT VALUE	SECTION & PARAGRAPH #	VALUE	SECTION & PARAGRAPH #
example	1a	one-way ANOVA	Fig. legend	9, 9, 10, 15	mice from at least 3 litters/group	Methods para 8	error bars are mean +/- SEM	Fig. legend	p = 0.044	Fig. legend	F(3, 36) = 2.97	Fig. legend
example	results, para 6	unpaired t-test	Results para 6	15	slices from 10 mice	Results para 6	error bars are mean +/- SEM	Results para 6	p = 0.0006	Results para 6	t(28) = 2.808	Results para 6

		TEST USED		n			DESCRIPTIVE STATS (AVERAGE, VARIANCE)		P VALUE		DEGREES OF FREEDOM & F/t/z/R/ETC VALUE	
	FIGURE NUMBER	WHICH TEST?	SECTION & PARAGRAPH #	EXACT VALUE	DEFINED?	SECTION & PARAGRAPH #	REPORTED?	SECTION & PARAGRAPH #	EXACT VALUE	SECTION & PARAGRAPH #	VALUE	SECTION & PARAGRAPH #
+ -	5a mTau (released tau)	Unpaired t-test with Satterthwaite's correction and Bonferroni adjustment.	Methods and Fig. legend	9	Two treatment groups. Each group contains cells on 9 separate coverslips as independent samples.	Fig. Legend	error bars are mean + / - SEM	Methods	adjusted p = 0.003	Fig. legend	t(9.167)=-4.75	Fig. legend
+ -	5a hTau + mTau (released tau)	Unpaired t-test with Bonferroni adjustment.	Methods and Fig. legend	9	Two treatment groups. Each group contains cells on 9 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM		adjusted p < 0.0001	Fig. legend	t(16)=-7.25	Fig. legen
+ -	5a hTau (released tau)	Unpaired t-test with Bonferroni adjustment.	Methods and Fig. legend	6	Two treatment groups. Each group contains cells on 6 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	adjusted p = 0.044	Fig. legend	t10)=-2.95	Fig. legen
+ -	5b mTau (LDH)	Unpaired t-test with Bonferroni adjustment.	Methods and Fig. legend	9	Two treatment groups. Each group contains cells on 9 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	adjusted p = 0.730	Fig. legend	t(16) =-1.22	Not reported
+ -	5b mTau + hTau (LDH)	Unpaired t-test with Bonferroni adjustment.	Methods and Fig. legend	9	Two treatment groups. Each group contains cells on 9 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	adjusted p = 0.061	Fig. legend	t(16) =-2.58	Not reported
+ -	5b hTau (LDH)	Unpaired t-test with Bonferroni adjustment.	Methods and Fig. legend	6	Two treatment groups. Each group contains cells on 6 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	adjusted p = 0.233	Fig. legend	t(16) =-1.97	Not reported
+ -	5g Tau (released tau)	Kruskal-Wallis, with Dunn's post hoc test and Bonferroni adjustment.	Methods and Fig. legend	4	Three groups. Each group contains cells on 4 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	p = 0.024 post hoc p=0.036 and p=0.021	Fig. legend	$\chi2(2)=7.42$	Fig. legend
+ -	5h Tau (LDH)	Kruskal-Wallis.	Methods and Fig. legend	4	Three groups. Each group contains cells on 4 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	p = 0.694	Fig. legend	$\chi2(2)=0.73$	Fig. legend
+ -	6b	Unpaired t-test	Methods and Fig. legend	5	Two treatment groups. Each group contains cells on 5 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	p = 0.028	Fig. legend	t(8) =-2.68	Fig. legend

+ -	7h	Wilcoxon rank sun test	Methods and Fig. legend	4	4 animals per group (tau and tau-KO)	Fig. legend	error bars are mean + / - SEM	Methods	p=0.021	Fig. legend	z=-2.309	Fig. legend
+ -	S1	Paired t-test	Methods	6	6 Paired samples from n=6 animals	Fig. legend	Ratio gene of interest/control gene	Fig. legend	p=0.18	Fig. legend	t(5)=-1.57	Fig. legend
+ -	4b control versus 1-6 hours)	Wilcoxon rank sun test plus Bonferroni adjustment.	Methods and Fig. legend	4, 6	Two groups (control and incubation group) Each group contains cells on 4 or 6 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	Adjusted p=0.021	Fig. legend	z =-2.558	Fig. legend
+ -	4b control versus 1-6 days)	Wilcoxon rank sun test plus Bonferroni adjustment.	Methods and Fig. legend	4, 4	Two groups (control and incubation group) Each group contains cells on 4 separate coverslips as independent samples.	Fig. legend	error bars are mean + / - SEM	Methods	Adjusted p=0.042	Fig. legend	z=-2.309	Fig. legend

Representative figures

1. Are any representative images shown (including Western blots and immunohistochemistry/staining) in the paper?

   If so, what figure(s)?

Representative images of confocal images:
Fig.1b,c, Fig. 2, 3, Fig. 4c, d, e, f, Fig. 5c,d, Fig. 6a, Fig. 7c-g, Fig. 8a, c, Supplementary Fig. 3, Supplementary Fig. 3a

immunoblots:
Fig. 4a

immunohistochemistry:
Fig. 7f, g, Fig.8b, Supplementary Fig. 3b

2. For each representative image, is there a clear statement of how many times this experiment was successfully repeated and a discussion of any limitations in repeatability?

   If so, where is this reported (section, paragraph #)?

Yes. Each representative figure is one of the figures that are shown. The number of cultures of neurons (n) and the total number of mice (n) are stated in figure legends of each individual figure.

Fig. 1a, b, reproduced in 4 coverslips of culture.
Fig. 2, reproduced in 4 coverslips of culture
Fig. 3b, c, reproduced in 3 coverslips of culture
Fig. 3e, reproduced in 2 coverslips of culture
Fig. 4c, reproduced in 4 coverslips of culture
Fig. 4f, reproduced in 2 coverslips of culture
Fig. 4d, e, reproduced in 3 coverslips of culture
Fig. 5c, d, reproduced in 4 coverslips of culture
Fig. 6a, reproduced in 5 coverslips of culture
Fig. 7c-f, reproduced in 2 animals.
Fig. 7g-h, reproduced in 4 animals.
Fig. 8, reproduced in 3 animals.

Statistics and general methods

1. Is there a justification of the sample size? If so, how was it justified? Where (section, paragraph #)? Even if no sample size calculation was performed, authors should report why the sample size is adequate to measure their effect size.	No statistical methods were used to predetermine sample sizes, but our sample sizes are similar to those previously reported. This is in Method, Statistical analysis section, paragraph #1. In the case of human iPSC neurons, because of limited availability (takes over 150 days in culture), we performed the experiment using 6 cultures of neurons. Sample sizes are reported in Figure legends additionally.
2. Are statistical tests justified as appropriate for every figure? Where (section, paragraph #)?	We performed statistical tests on data in Fig. 4b, 5a, b, g, h, Fig 6b and 7h, and Supplementary Figure 1, and justified each test appropriately (Method, Statistical analysis section, paragraph #16).
a. If there is a section summarizing the statistical methods in the methods, is the statistical test for each experiment clearly defined?	The statistical tests for each experiment is defined in Methods, Statistical Analyses section.
b. Do the data meet the assumptions of the specific statistical test you chose (e.g. normality for a parametric test)? Where is this described (section, paragraph #)?	Tau and LDH release (Fig. 5a,b), plus tau uptake (Fig 6b) were assessed for normality and were shown to be normally distributed. When sample sizes were <=4, tests for normality were not performed and non-parametric tests were employed. Analyses are described in Methods, Statistical Analysis section, paragraph #16.
c. Is there any estimate of variance within each group of data? Is the variance similar between groups that are being statistically compared? Where is this described (section, paragraph #)?	Yes, we used Levene's test for homogeneity of variances for Fig.5 (a and b) and Fig 6 (b), followed by Satterthwaite's approximation for unequal group variance when necessary (Fig. 5a). This is described in detail in the Methods Section, Statistical Analysis.
d. Are tests specified as one- or two-sided?	All tests are two-sided.
e. Are there adjustments for multiple comparisons?	Adjustments were made for multiple comparisons using Bonferroni adjustments for data in 4b, Fig 5 a, b, and g.
3. To promote transparency, *Nature Neuroscience* has stopped allowing bar graphs to report statistics in the papers it publishes. If you have bar graphs in your paper, please make sure to switch them to dot-plots (with central and dispersion statistics displayed) or to box-and-whisker plots to show data distributions.	All graphs are in dot-plots.
4. Are criteria for excluding data points reported? Was this criterion established prior to data collection? Where is this described (section, paragraph #)?	NA

5. Define the method of randomization used to assign subjects (or samples) to the experimental groups and to collect and process data. If no randomization was used, state so. Where does this appear (section, paragraph #)?	Mice of the appropriate age were selected from 2 different litters and randomly assigned as control or experimental for in vivo stimulations (Fig. 7, 8). Mice were randomly assigned for RT PCR experiment (Supp Figure 1). This is described in Method, Statistical method section, paragraph #1.
6. Is a statement of the extent to which investigator knew the group allocation during the experiment and in assessing outcome included? If no blinding was done, state so. Where (section, paragraph #)?	Immunofluorescence images were quantified by a blinded observer. Optogenetic stimulation was carried out by a blinded observer. Separate blinded authors analyzed DAB and immunofluorescence stains of brain tissues (non stimulated hemisphere vs stimulated hemisphere). This is described in Methods, Statistical methods.
7. For experiments in live vertebrates, is a statement of compliance with ethical guidelines/regulations included? Where (section, paragraph #)?	Compliance with ethical guidelines are included in Method section, Transgenic mice section, paragraph #1 and under Surgery, paragraph #11.
8. Is the species of the animals used reported? Where (section, paragraph #)?	Yes. Method section, Transgenic mice section, paragraph #1.
9. Is the strain of the animals (including background strains of KO/ transgenic animals used) reported? Where (section, paragraph #)?	Yes. Strain and background of mice are stated in main manuscript, labeled in figures, and described in Method section, Transgenic mice section, paragraph #1.
10. Is the sex of the animals/subjects used reported? Where (section, paragraph #)?	Mixed sex were used.
11. Is the age of the animals/subjects reported? Where (section, paragraph #)?	The age of mice are stated in Method, Animals section, paragraph #1.
12. For animals housed in a vivarium, is the light/dark cycle reported? Where (section, paragraph #)?	Mice were housed in a vivarium, individually housed.
13. For animals housed in a vivarium, is the housing group (i.e. number of animals per cage) reported? Where (section, paragraph #)?	NA
14. For behavioral experiments, is the time of day reported (e.g. light or dark cycle)? Where (section, paragraph #)?	NA
15. Is the previous history of the animals/subjects (e.g. prior drug administration, surgery, behavioral testing) reported? Where (section, paragraph #)?	NA

a. If multiple behavioral tests were conducted in the same group of animals, is this reported?

Where (section, paragraph #)?

NA

16. If any animals/subjects were excluded from analysis, is this reported?

Where (section, paragraph #)?

NA

a. How were the criteria for exclusion defined?

Where is this described (section, paragraph #)?

b. Specify reasons for any discrepancy between the number of animals at the beginning and end of the study.

Where is this described (section, paragraph #)?

Reagents

1. Have antibodies been validated for use in the system under study (assay and species)?

Yes.

a. Is antibody catalog number given?

Where does this appear (section, paragraph #)?

Name and source of antibodies are provided in the main manuscript and in Method section, paragraph #14.

b. Where were the validation data reported (citation, supplementary information, Antibodypedia)?

Where does this appear (section, paragraph #)?

All commercial and non-commercial antibodies have been validated in previous publications. Select representative publications are cited in the Reference section.

2. Cell line identity

a. Are any cell lines used in this paper listed in the database of commonly misidentified cell lines maintained by ICLAC and NCBI Biosample?

Where (section, paragraph #)?

No cell lines were used.

The cell models used for this study were primary neurons and human induced pluripotent stem cells.

b. If yes, include in the Methods section a scientific justification of their use--indicate here in which section and paragraph the justification can be found.

Primary neurons, described in Method section, paragraph #2. Human induced pluripotent stem cells , described in Method section, paragraph #3 and in citation.

c. For each cell line, include in the Methods section a statement that specifies:

- the source of the cell lines
- have the cell lines been authenticated? If so, by which method?
- have the cell lines been tested for mycoplasma contamination?

Where (section, paragraph #)?

Usage of these two cell model are reported in Methods, paragraph #1,2, and in citations.

The two cell models used are not cell lines and were not tested for mycoplasma contamination.

Data availability

Provide a Data availability statement in the Methods section under "Data availability", which should include, where applicable:

- Accession codes for deposited data
- Other unique identifiers (such as DOIs and hyperlinks for any other datasets)
- At a minimum, a statement confirming that all relevant data are available from the authors
- Formal citations of datasets that are assigned DOIs
- A statement regarding data available in the manuscript as source data
- A statement regarding data available with restrictions

See our data availability and data citations policy page for more information.

Data deposition in a public repository is mandatory for:

a. Protein, DNA and RNA sequences
b. Macromolecular structures
c. Crystallographic data for small molecules
d. Microarray data

Deposition is strongly recommended for many other datasets for which structured public repositories exist; more details on our data policy are available here. We encourage the provision of other source data in supplementary information or in unstructured repositories such as Figshare and Dryad.

We encourage publication of Data Descriptors (see Scientific Data) to maximize data reuse.

Where is the Data Availability statement provided (section, paragraph #)?

Data availability statement regarding availability and source data is provided in Methods under Data availability.

NA for data deposition.

Computer code/software

Any custom algorithm/software that is central to the methods must be supplied by the authors in a usable and readable form for readers at the time of publication. However, referees may ask for this information at any time during the review process.

1. Identify all custom software or scripts that were required to conduct the study and where in the procedures each was used.

Volocity was used to process confocal microscopy images and for 3D analysis of tau localization. Spike sorting software Tint (Axona) and sigTOOL (a Matlab-based signal analysis tool) were used to sort neurons and visualize changes in spike firing rate during optical stimulation.

2. If computer code was used to generate results that are central to the paper's conclusions, include a statement in the Methods section under "**Code availability**" to indicate whether and how the code can be accessed. Include version information as necessary and any restrictions on availability.

All used software, Volocity, Tint, and sigTOOL, source, and the usage are provided in the Method section of the manuscript.
Tint is a proprietary software and can be obtained from www.axona.com
sigTOOL is a free tool and can be obtained from http://sourceforge.net/projects/sigtool/

Human subjects

1. Which IRB approved the protocol?

   Where is this stated (section, paragraph #)?

   NA

2. Is demographic information on all subjects provided?

   Where (section, paragraph #)?

3. Is the number of human subjects, their age and sex clearly defined?

   Where (section, paragraph #)?

4. Are the inclusion and exclusion criteria (if any) clearly specified?

   Where (section, paragraph #)?

5. How well were the groups matched?

   Where is this information described (section, paragraph #)?

6. Is a statement included confirming that informed consent was obtained from all subjects?

   Where (section, paragraph #)?

7. For publication of patient photos, is a statement included confirming that consent to publish was obtained?

   Where (section, paragraph #)?

fMRI studies

For papers reporting functional imaging (fMRI) results please ensure that these minimal reporting guidelines are met and that all this information is clearly provided in the methods:

1. Were any subjects scanned but then rejected for the analysis after the data was collected?

   NA

   a. If yes, is the number rejected and reasons for rejection described?

      Where (section, paragraph #)?

2. Is the number of blocks, trials or experimental units per session and/or subjects specified?

   Where (section, paragraph #)?

3. Is the length of each trial and interval between trials specified?

4. Is a blocked, event-related, or mixed design being used? If applicable, please specify the block length or how the event-related or mixed design was optimized.

5. Is the task design clearly described?

   Where (section, paragraph #)?

6. How was behavioral performance measured?

7. Is an ANOVA or factorial design being used?

8. For data acquisition, is a whole brain scan used?

   If not, state area of acquisition.

   a. How was this region determined?

9. Is the field strength (in Tesla) of the MRI system stated?

   a. Is the pulse sequence type (gradient/spin echo, EPI/spiral) stated?

   b. Are the field-of-view, matrix size, slice thickness, and TE/TR/flip angle clearly stated?

10. Are the software and specific parameters (model/functions, smoothing kernel size if applicable, etc.) used for data processing and pre-processing clearly stated?

11. Is the coordinate space for the anatomical/functional imaging data clearly defined as subject/native space or standardized stereotaxic space, e.g., original Talairach, MNI305, ICBM152, etc? Where (section, paragraph #)?

12. If there was data normalization/standardization to a specific space template, are the type of transformation (linear vs. nonlinear) used and image types being transformed clearly described? Where (section, paragraph #)?

13. How were anatomical locations determined, e.g., via an automated labeling algorithm (AAL), standardized coordinate database (Talairach daemon), probabilistic atlases, etc.?

14. Were any additional regressors (behavioral covariates, motion etc) used?

15. Is the contrast construction clearly defined?

16. Is a mixed/random effects or fixed inference used?

   a. If fixed effects inference used, is this justified?

17. Were repeated measures used (multiple measurements per subject)?

a. If so, are the method to account for within subject correlation and the assumptions made about variance clearly stated?

18. If the threshold used for inference and visualization in figures varies, is this clearly stated?

19. Are statistical inferences corrected for multiple comparisons?

a. If not, is this labeled as uncorrected?

20. Are the results based on an ROI (region of interest) analysis?

a. If so, is the rationale clearly described?

b. How were the ROI's defined (functional vs anatomical localization)?

21. Is there correction for multiple comparisons within each voxel?

22. For cluster-wise significance, is the cluster-defining threshold and the corrected significance level defined?

Additional comments

Additional Comments	NA