nature research

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Last updated by author(s): Feb 24, 2020

Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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 (*n*) 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 *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 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. *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

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	FLUOVIEW 4.1.1.5 (Olympus FV1200MPE microscope), LAS X 3.1.5.16308 (Leica TCS SP8 microscope), and Raspbian 9 and Python 2.7.13 (controlling the custom-built cyclic compression device)
Data analysis	ImageJ 1.52 (image projection and video making), IMARIS 7 (three-dimensional image rendering), and custom MATLAB (2016a) codes for diffusion modeling, and Python 3.6 (depth-wise immunoreactivity comparison). The codes used for deformation analysis are described in Ku et al. Nat Biotechnol (2016).

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. 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

The data supporting the findings of this study are available from the corresponding author upon request.

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

Life sciences study design

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

Sample size	No sample-size calculation was performed, and either three, four, five, or six was chosen with considering a previous report in a relevant design (Ku et al. Nat Biotechnol, 2016).
Data exclusions	No data were excluded from the analyses.
Replication	All experiments were repeated at least twice with the same conclusions. One exception is the thick-tissue labeling, which was performed once but not following and followed by unsuccessful cases in the aimed experimental setting.
Randomization	All samples were randomly assigned to groups. One exception is the ELAST tissue samples subjected to thickness measurement after stretching and/or contraction, which were divided into two groups so as to have average thicknesses closest to each other for the fairest comparison.
Blinding	Since all randomly assigned samples had no pre-recognizable factors, no blinding was used.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used

anti-NeuN antibody (ab104225, Abcam), 1:300
anti-NeuN antibody (834501, BioLegend), 1:300
anti-NeuN antibody (MAB377, Millipore), 1:300
anti-calbindin antibody (13176S, Cell Signaling), 1:300
anti-calretinin antibody (ab702, Abcam), 1:300 (mouse), 10:1,000 (human)
anti-calretinin antibody (CPCA-Calret, EnCor), 1:300
anti-parvalbumin antibody (PA1-933, Invitrogen), 1:300
anti-tyrosine hydroxylase antibody (13106S, Cell Signaling), 1:300
anti-tyrosine hydroxylase antibody (818001, BioLegend), 1:300
anti-neuropeptide Y antibody (11976S, Cell Signaling), 1:300
anti-SMI-32 antibody (801704, BioLegend), 1:300
anti-SMI-312 antibody (837904, BioLegend), 1:300 (mouse), 2:300 (human)
anti-neurofilament light chain antibody (2837S, Cell Signaling), 1:300
anti-neurofilament light chain antibody (NFL, Aves), 60:1,000
anti-neurofilament medium chain antibody (NFM, Aves), 1:300
anti-MAP2 antibody (ab32454, Abcam), 1:300
anti-MAP2 antibody (ab5392, Abcam), 1:300
anti-MAP2 antibody (822501, BioLegend), 1:300
anti-MAP2 antibody (677807, BioLegend), 10:1,000
anti-myelin basic protein antibody (ab7349, Abcam), 1:300 (mouse), 2:300 (human)
anti-myelin basic protein antibody (MBP, Aves), 1:300
anti-TUJ1 antibody (801201, BioLegend), 1:300

anti-iba1 antibody (ab178847, Abcam), 1:300
anti-glial fibrillary acidic protein antibody (8152S, Cell Signaling), 1:300 (mouse), 3:300 (human), 10:1,000 (human), 50:5,000 (human)
anti-glial fibrillary acidic protein antibody (644704, BioLegend), 3:300, 20:2,000
anti-green fluorescent protein antibody (A10262, Invitrogen), 1:300
anti-green fluorescent protein antibody (A31852, Invitrogen), 1:300
anti-histone H3 antibody (819406, BioLegend), 1:300
anti-histone H3 antibody (4499S, Cell Signaling), 1:300
anti-synapsin 1/2 antibody (106002, Synaptic Systems), 1:300
anti-PSD-95 antibody (75-028, NeuroMab), 1:300
anti-vimentin antibody (801803, BioLegend), 4:1,000

Validation

anti-NeuN antibodies (ab104225, 834501, MAB377) on mouse: cross-validated on the same tissue samples; Ku et al. Nat Biotechnol (2016).
anti-NeuN antibody (ab104225) on human: Murray et al. Cell (2015).
anti-calbindin antibody (13176S) on mouse: Ku et al. Nat Biotechnol (2016).
anti-calbindin antibody (13176S) on human: Murray et al. Cell (2015).
anti-calretinin antibodies (ab702, CPCA-Calret) on mouse: cross-validated on the same tissue samples; Ku et al. Nat Biotechnol (2016).
anti-calretinin antibody (ab702) on human: Murray et al. Cell (2015).
anti-parvalbumin antibody (PA1-933) on mouse: Ku et al. Nat Biotechnol (2016).
anti-parvalbumin antibody (PA1-933) on human: Murray et al. Cell (2015).
anti-tyrosine hydroxylase antibodies (13106S, 818001) on mouse: cross-validated on the same tissue samples; Ku et al. Nat Biotechnol (2016).
anti-tyrosine hydroxylase antibody (818001) on human: Murray et al. Cell (2015).
anti-SMI-32 antibody (801704) on mouse: Ku et al. Nat Biotechnol (2016).
anti-SMI-312 antibody (837904) on mouse: Ku et al. Nat Biotechnol (2016).
anti-SMI-312 antibody (837904) on human: Murray et al. Cell (2015).
anti-neurofilament light chain antibody (2837S) on mouse: Ku et al. Nat Biotechnol (2016).
anti-neurofilament light chain antibody (NFL) on human: Ku et al. Nat Biotechnol (2016).
anti-neurofilament medium chain antibody (NFM) on mouse: Ku et al. Nat Biotechnol (2016).
anti-MAP2 antibodies (ab32454, ab5392) on mouse: cross-validated on the same tissue samples; Ku et al. Nat Biotechnol (2016).
anti-MAP2 antibody (822501) on human: cross-validated with ab32454 (Abcam); Ku et al. Nat Biotechnol (2016).
anti-MAP2 antibody (677807) on cerebral organoids: Lancaster et al. Nature (2013).
anti-myelin basic protein antibodies (ab7349, MBP) on mouse: cross-validated on the same tissue samples; Ku et al. Nat Biotechnol (2016).
anti-myelin basic protein antibody (ab7349) on human: Murray et al. Cell (2015).
anti-TUJ1 antibody (801201) on mouse: Ku et al. Nat Biotechnol (2016).
anti-iba1 antibody (ab178847) on mouse: Park et al. Nat Biotechnol (2019).
anti-glial fibrillary acidic protein antibody (8152S) on mouse: Ku et al. Nat Biotechnol (2016).
anti-glial fibrillary acidic protein antibodies (8152S, 644704) on human: cross-validated on the same tissue samples; Murray et al. Cell (2015).
anti-green fluorescent protein antibodies (A10262, A31852) on mouse: cross-validated on the same tissue samples; Ku et al. Nat Biotechnol (2016).
anti-histone H3 antibodies (819406, 4499S) on mouse: cross-validated on the same tissue samples; Ku et al. Nat Biotechnol (2016).
anti-synapsin 1/2 antibody (106002) and anti-PSD-95 antibody (75-028) on human: Ku et al. Nat Biotechnol (2016); the characteristic close alignment of pre- and post-synaptic structures was confirmed.
anti-vimentin antibody (801803) on cerebral organoids: Lancaster et al. Nature (2013).

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Male and female 2–4-month-old Thy1-GFP-M transgenic mice were used.
Wild animals	The current study did not involve wild animals.
Field-collected samples	The current study did not involve field-collected samples.
Ethics oversight	The MIT Institutional Animal Care and Use Committee and the Division of Comparative Medicine approved the protocol.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	The current study did not involve living human participants and used autopsy brains banked at the Neuropathology Core of the Massachusetts Alzheimer Research Center. The current study design did not consider specific types of human population.
Recruitment	Banked autopsy brains were provided. Since the current study did not deal with biological or medical findings, there are no potential selection-biases to state.

Ethics oversight	The Institutional Review Board of the Massachusetts General Hospital

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