nature portfolio

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Reporting Summary

Nature Portfolio 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 Portfolio policies, see our Editorial Policies 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	Data from single nucleus RNAseq is available under GSE259430. Bioluminescence imaging and analysis was performed using IVIS® Lumina III In Vivo Imaging System. Laser Doppler Imaging was performed using MOORLDI2-IR. Confocal imaging was performed using Leica SP8 laser confocal and the Zeiss Axio Scan.Z1 slide scanner was used to determine stroke volume.
Data analysis	Fiji (ImageJ) was used for image data processing. A custom-made RScript was used for behavioral analysis previously published: PMID: 36243716. Single cell RNAseq (stored under GSE259430) was analysed using R according to the Seurat 5 guidelines (PMID: 29608179,PMID: 37231261).

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data from single nucleus RNAseq is available under GSE259430. Other raw data that support the findings of this study are available from the corresponding author upon request.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used. Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status). Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.) Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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

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	Sample sizes were estimated based on previous publications from our lab and pilot studies.
Data exclusions	No mice were excluded from the analyses.
Replication	For each experiment, at least 3 animals or 3 cell cultures replicates were used. For each series of experiments, all replication attempts were successful. The N number is also indicated in the respective figures.
Randomization	All animals were randomized for their treatment group.
Blinding	Experiments were blinded: the operators responsible for the experimental procedures and data analysis were blinded and unaware of group allocation in the experiments.

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 and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used

Antigen Target Host Dilution Company
CD 13: Pericytes goat 1:200 R&D Systems, AF2335
CD 31: Vascular endothelial cells rat 1:50 BD Biosciences, 550274
fibrinogen Blood vessel leakage rabbit 1:100 abcam, ab34269
HuNu Human nuclei mouse 1:200 EMD Millipore, clone 235-1
Ki-67 Marker for cell cycling and proliferation; tumor marker rabbit 1:200 Invitrogen, MA5-14520
hNanog Pluripotency marker goat 1:30 R&D Systems, AF1997
GFAP Astrocytes mouse 1:200 R&D Systems, MAB2594
MAP2 Neurons mouse 1:200 R&D Systems, MAB8304
Pax6 Neural progenitor cells rabbit 1:40 R&D Systems, AF8150
Iba1 Microglia goat 1:200, Abcam: ab5076
Casp-3 Apoptopic cells rabbit Asp175 1:200 Cell Signaling
NeuN Neurons mouse A60 1:200 Abcam
hNCAM Graft-derived neurites rabbit EPR21827 1:10000 Abcam
Olig-2 Oligodendrocyte precursor cells rabbit EPR2673 1:50 Abcam
NF-L Neurofilament light chain guinea pig 171□004 1:250 Synaptic Systems
NF-H Neurofilament heavy chain rabbit N4142 1:100 Sigma
VIP Interneurons rabbit 9J9H3 1:300 Invitrogen
SST Interneurons rat YC7 1:500 Milipore
PVALB Interneurons rabbit MA5□47410 1:250 Invitrogen
Synaptophysin Presynaptic vesicles rabbit SP11 1:200 Invitrogen

Validation

The antibodies were validated by the supplier and in our previous studies PMID: 31235580, PMID: 31882970, PMID: 36114512:

CD13: https://www.rndsystems.com/products/mouse-aminopeptidase-n-cd13-antibody_af2335
CD31: https://www.bdbiosciences.com/en-us/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/purified-rat-anti-mouse-cd31.550274
Fibrinogen: https://www.abcam.com/products/primary-antibodies/fibrinogen-antibody-ab34269.html
HuNu: https://www.emdmillipore.com/US/en/product/Anti-Nuclei-Antibody-clone-235-1,MM_NF-MAB1281?ReferrerURL=https%3A%2F%2Fwww.google.com%2F
Ki-67: https://www.thermofisher.com/antibody/product/Ki-67-Antibody-clone-SP6-Recombinant-Monoclonal/MA5-14520
hNanog: https://www.rndsystems.com/products/human-nanog-antibody_af1997
GFAP: https://www.rndsystems.com/products/human-gfap-antibody-273807_mab2594
MAP2: https://www.rndsystems.com/products/human-map2-antibody-885232_mab8304
Pax6: https://www.rndsystems.com/products/human-pax6-antibody_af8150
Iba1: https://www.abcam.com/products/primary-antibodies/iba1-antibody-ab5076.html
Casp-3: https://www.cellsignal.com/products/primary-antibodies/caspase-3-antibody/9662
NeuN: https://www.abcam.com/neu-n-antibody-a60-ab104224.html
hNCAM: https://www.abcam.com/ncam1-antibody-epr21827-ab220360.html
Olig-2: https://www.abcam.com/olig2-antibody-epr2673-oligodendrocyte-marker-ab109186.html
NF-L: https://www.sysy.com/product/171004
NF-H: https://www.sigmaaldrich.com/US/en/product/sigma/n4142
VIP: https://www.thermofisher.com/antibody/product/VIP-Antibody-clone-9J9H3-Recombinant-Monoclonal/MA5-58176
SST: https://www.sigmaaldrich.com/US/en/product/mm/mab354
PVALB: https://www.thermofisher.com/antibody/product/Parvalbumin-Antibody-Recombinant-Monoclonal/MA5-47410
Synaptophysin: https://www.thermofisher.com/antibody/product/Synaptophysin-Antibody-clone-SP11-Monoclonal/MA5-14532

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	NPCs were generated from iPSC under feeder-free and xeno-free conditions. iPSC were derived from peripheral blood mononuclear cells as previously reported: PMID: 36114512, PMID: 36447645
Authentication	iPSC and NPCs were previously characterised in a separate publication for expression of canonical marker: PMID: 36114512
Mycoplasma contamination	Cell lines were tested for mycoplasma contamination. All cells were negative for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	adult (3-4 months) male and female genetically immunodeficient Rag2-/- mice were used
Wild animals	This study did not involve wild animals.
Reporting on sex	Both male and female mice were used in the study.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	All animal experiments were performed at the Laboratory Animal Services Center (LASC) in Schlieren according to the local guidelines for animal experiments and were approved by the Veterinary Office in Zurich, Switzerland.

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

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*