

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

Plate reader Flex station III,
Zeiss Axio Imager 2, Zeiss ZEN imaging (2020)
Leica SP8 confocal microscope
Rotor Gene® (Qiagen) Q v2.3.1

Data analysis

ImageJ 1.32J software NIH <https://imagej.nih.gov/>
G*Power (v3.1) <https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html>
Research Randomizer <https://www.randomizer.org/>
GraphPad Prism 8, Software Inc. <https://www.graphpad.com/scientific-software/prism/>
Plate reader Flex station III, SoftMax Pro 7 Data Acquisition and Analysis Software
Rotor Gene® Q software (v.2.3.1.49).
LAS X imaging software Coral Cryo
SoftMax Pro v7.1 Data Acquisition and Analysis Software

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](#)

All materials generated in this study are available from Francesco De Logu (Francesco.delogu@unifi.it) and Romina Nassini (romina.nassini@unifi.it). The data generated in this study are provided in the Supplementary Information/Source Data file.

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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](https://www.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	The group size of n = 8 animals for behavioral experiments was determined by sample size estimation using G*Power (v3.1) to detect size effect in a post-hoc test with type 1 and 2 error rates of 5 and 20%, respectively.
Data exclusions	No animals were excluded from experiments
Replication	Experimental findings were reliably reproduced among all experiments. The detailed information is reported throughout the figure legends.
Randomization	Allocation concealment of mice into the vehicle(s) or treatment groups was performed using a randomization procedure (http://www.randomizer.org/).
Blinding	The assessors were blinded to the identity of the animals (genetic background) or allocation to treatment groups.

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

1. EP2 (#ab167171, rabbit monoclonal, Abcam, 1:250)
2. EP4 (#BS-8538R, rabbit polyclonal, Bioss, 1:200)
3. S100B (#MA1-26621, mouse monoclonal, Invitrogen, 1:50)
4. NeuN (#MAB377, mouse monoclonal, Merck, 1:250)
5. Alexa Fluor® 488 (#A32731, goat polyclonal anti-rabbit, Invitrogen, 1:600)
6. Alexa Fluor® 594 (#A11005, goat polyclonal anti-mouse, Invitrogen, 1:600)
7. EP4 (#sc-55596, mouse monoclonal, Santa Cruz, 1:50)
8. Alexa Fluor® 488 Anti-S100B antibody (#ab196442, rabbit monoclonal, Abcam, 1:100)
9. Alexa Fluor® 594 (#A21207, donkey polyclonal anti rabbit, Invitrogen, 1:600)
10. Alexa Fluor® 594 (#A11005, goat polyclonal anti mouse, Invitrogen, 1:600)
11. Sox10 (#AF2864, goat polyclonal, R&D Systems, 1:100)
12. Alexa Fluor® 594 (#A11058, donkey polyclonal anti-goat, Invitrogen, 1:600)
13. GFP (#A6455, rabbit polyclonal, Invitrogen, 1:600)
14. Alexa Fluor® 488 (#A32790, donkey polyclonal anti rabbit, Invitrogen, 1:600)
15. Glutamine Synthetase (#AB64613, mouse monoclonal, Abcam, 1:1000)
16. Alexa Fluor® 647 Anti-S100 beta antibody [EP1576Y] (#ab196175, rabbit monoclonal, Abcam, 1:50)

Validation

1. EP2 (#ab167171, rabbit monoclonal, Abcam, 1:250)
<https://www.abcam.com/en-us/products/primary-antibodies/prostaglandin-e-receptor-ep2-ptger2-antibody-epr8030b-ab167171#>
2. EP4 (#BS-8538R, rabbit polyclonal, Bioss, 1:200)
<https://www.biossusa.com/products/bs-8538r?srltid=AfmBOorJhbl1cx0dq0ukiUU0zcmTJpXHpwUY7O7W2cYcipXd3Wlm6->
3. S100B (#MA1-26621, mouse monoclonal, Invitrogen, 1:50)
<https://www.thermofisher.com/antibody/product/S100-Antibody-clone-4C4-9-Monoclonal/MA1-26621>
4. NeuN (#MAB377, mouse monoclonal, Merck, 1:250)
<https://www.sigmaldrich.com/IT/it/product/mm/mab377>
5. Alexa Fluor® 488 (#A32731, goat polyclonal anti-rabbit, Invitrogen, 1:600)
<https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A32731>
6. Alexa Fluor® 594 (#A11005, goat polyclonal anti-mouse, Invitrogen, 1:600)
<https://www.thermofisher.com/antibody/product/Goat-anti-Mouse-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11005>
7. EP4 (#sc-55596, mouse monoclonal, Santa Cruz, 1:50)
https://www.scbt.com/p/ep4-antibody-c-4?srltid=AfmBOoqLIZMc95IonZlxop84eXG5oSbxUIKJV93I5ZSD1_1j266jRaVd
8. Alexa Fluor® 488 Anti-S100B antibody (#ab196442, rabbit monoclonal, Abcam, 1:100)
<https://www.abcam.com/en-us/products/primary-antibodies/alexa-fluor-488-s100-beta-antibody-ep1576y-ab310990>
9. Alexa Fluor® 594 (#A21207, donkey polyclonal anti rabbit, Invitrogen, 1:600)
<https://www.thermofisher.com/antibody/product/Donkey-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21207>
10. Alexa Fluor® 594 (#A11005, goat polyclonal anti mouse, Invitrogen, 1:600)
<https://www.thermofisher.com/antibody/product/Goat-anti-Mouse-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11005>

11. Sox10 (#AF2864, goat polyclonal, R&D Systems, 1:100)
[https://www.bio-technie.com/p/antibodies/human-sox10-antibody_af2864?](https://www.bio-technie.com/p/antibodies/human-sox10-antibody_af2864?utm_source=citeab&utm_medium=referral&utm_campaign=product&utm_term=primaryantibodies)
 utm_source=citeab&utm_medium=referral&utm_campaign=product&utm_term=primaryantibodies
12. Alexa Fluor® 594 (#A11058, donkey polyclonal anti-goat, Invitrogen, 1:600)
<https://www.thermofisher.com/antibody/product/Donkey-anti-Goat-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11058>
13. GFP (#A6455, rabbit polyclonal, Invitrogen, 1:600)
<https://www.thermofisher.com/antibody/product/A-6455.html?CID=AFLCA-A-6455>
14. Alexa Fluor® 488 (#A32790, donkey polyclonal anti rabbit, Invitrogen, 1:600)
<https://www.thermofisher.com/antibody/product/Donkey-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A32790>
15. Glutamine Synthetase (#AB64613, mouse monoclonal, Abcam, 1:1000)
<https://www.abcam.com/en-us/products/primary-antibodies/glutamine-synthetase-antibody-3b6-bsa-and-azide-free-ab64613>
16. Alexa Fluor® 647 Anti-S100 beta antibody [EP1576Y] (#ab196175, rabbit monoclonal, Abcam, 1:50)
<https://www.abcam.com/en-us/products/primary-antibodies/alexa-fluor-647-s100-beta-antibody-ep1576y-astrocyte-marker-ab196175>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	Human Schwann cells (#P10351; Innoprot) AAVpro 293T cells (#632273, Takara, RRID:CVCL_B0XW) HEK 293T cells (#CRL-3216, ATCC, RRID:CVCL_0063)
Authentication	All cells were used when received without further authentication.
Mycoplasma contamination	Cell Lines were negative to 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	C57BL/6J (Charles River, RRID: IMSR_JAX:000664) male and female mice (25–30g, 6–8 weeks old) 129S-Trpa1tm2Kykw/J (floxed TRPA1, Trpa1fl/fl, RRID:IMSR_JAX:008649 Jackson Laboratory) mice (male 25-30 g, 6-8 weeks) B6.Cg-Tg(Plp1-CreERT)3Pop/J mice (Plp1-CreERT, RRID:IMSR_JAX:005975 Jackson Laboratory) mice (male 25-30 g, 6-8 weeks) Advillin-Cre mice (Adv-Cre) mice (male 25-30 g, 6-8 weeks) donate by Prof Al Basbaum University of California, US
Wild animals	N/A
Reporting on sex	Male and female mice were used. As no difference was found between male and female mice, to minimize the number of animals used, only key experiments were replicated in both sexes.
Field-collected samples	Mice were housed in a temperature- and humidity-controlled vivarium (12 hr dark/light cycle, free access to food and water, 5 animals per cage). At least 1 hr before behavioral experiments, mice were acclimatized to the experimental room and behavior was evaluated between 9:00 am and 5:00 pm. All the procedures were conducted following the current guidelines for laboratory animal care and the ethical guidelines for investigations of experimental pain in conscious animals set by the International Association for the Study of Pain (Zimmermann 1983, Pain 16, 109-110).
Ethics oversight	Animal experiments and sample collections were carried out according to the European Union (EU) guidelines for animal care procedures and Italian legislation (DLgs 26/2014) application of the EU Directive 2010/63/EU. All animal studies were approved by the Animal Ethics Committee of the University of Florence and the Italian Ministry of Health (permits no. 765/2019-PR, 288/2021-PR).

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

Plants

Seed stocks

N/A

Novel plant genotypes

N/A

Authentication

N/A