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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	Microscopy: ZEN2 software (Zeiss) RNA/DNA quality: 2100 Expert Software BulkRNAseq: NextSeq System Suite, HiSeq Control Software, Illumina bcl2fastq2 Conversion Software v2.17 scRNAseq: Illumina basespace platform qPCR: BioRad CFX manager See also methods section.
Data analysis	Microscopy: Image J (NIH) and Imaris v 8.2.1 (Bitplane) Electrophysiology: Mini Analysis Program Single-cell RNAseq: inDrops.py (https://github.com/indrops/indrops), Bowtie 1.1.1, Monocle2 (RStudio) and MATLAB (v r2016b, Mathworks). Bulk RNA seq: TopHat2, HTSeq-count (v0.6.0), SPEctRA, DESeq2 package v.1.6.3, R (v3.1.1), Enrichr, Multiple Experiment Viewer 4.8, Ingenuity Pathway Analysis Graphs and statistics: Excel v.15.05101.1000 (Microsoft Office Professional Plus 2013) and Prism v7.01, v5.01 (Graphpad) See also methods section.

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

All data that support the findings, tools, and reagents will be shared upon reasonable request. All requests should be directed to the corresponding author. All accession codes will be available after publication.

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 statistical methods were used to pre-determine sample sizes but our sample sizes are similar to those reported in previous publications.
Data exclusions	No data points were excluded from our analyses.
Replication	Findings were replicated by three researchers within the lab (authors Gunner, G, Johnson, K and Lotun, A) and all attempts at replication were successful. All analyses were performed blind as described in our Methods.
Randomization	Both female and male littermate mice were used in our study with random allocation of males and females to each genotype and condition, described in our Methods.
Blinding	All analyses were performed blind; file names/animal IDs/genotypes were coded when performing our data analysis for fluorescence intensity, synapse density, and engulfment.

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-CD68 (1:1000; cat# MCA1957; lot# 1708; AbD Serotec; Raleigh, NC)
anti-VGluT2 (1:2000; cat# AB2251; lot# 3101508; MilliporeSigma; Darmstadt, Germany)
anti-Iba-1 (1:1000; cat# 019-18741; lot# PTR2404; Wako Chemicals; Richmond, VA)
anti-Homer1 (1:1000; cat# 160003; lot# 160003/1-47; Synaptic Systems; Goettingen, Germany)
anti-APP (1:1000; cat# 51-2700; lot# SA243371; ThermoFisher Scientific; Waltham, MA)
anti-Cleaved Caspase 3 (1:200; cat# 9661; lot# 45; Cell Signaling Technology; Danvers, MA)
anti-ATF3 (1:500; cat# HPA001562; lot# B116285; Sigma-Aldrich; Darmstadt, Germany)
Anti-NeuN (1:1000; cat# ABN91; lot# 3132967; MilliporeSigma; Darmstadt, Germany)
anti-CD45 (1:100; cat# MCA1388; lot# 170621; Bio-Rad; Hercules, CA)
anti- ALDH1L1 clone N103/39 (1:1000; cat# MABN495; lot# 2943620; MilliporeSigma; Darmstadt, Germany)
anti- NG2 (1:200; cat# AB5320; lot# 3061186; MilliporeSigma; Darmstadt, Germany)

anti- P2RY12 (1:100; cat# 848002; lot# B244070; Bio-Rad; Hercules, CA)
anti- F4/80 (1:1000; cat# MA-91124; lot# SJ2459832O; Invitrogen-ThermoFisher Scientific;Waltham, MA)
Goat anti-Chicken IgG (H+L) Secondary Antibody, Alexa Fluor 488 conjugate (1:1000; cat# A-11039; lot# 1937504; ThermoFisher Scientific; Waltham MA)
Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 488 conjugate (1:1000; cat# A-11034; lot# 1971418; ThermoFisher Scientific; Waltham MA)
Goat anti-Guinea Pig IgG (H+L) Secondary Antibody, Alexa Fluor 594 conjugate (1:1000; cat# A-11076; lot# 1848493; ThermoFisher Scientific; Waltham MA)
Goat anti-Rat IgG (H+L) Secondary Antibody, Alexa Fluor 594 conjugate (1:1000; cat# A-11007; lot# 1807719; ThermoFisher Scientific; Waltham MA)
Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 594 conjugate (1:1000; cat# A-11037; lot# 1205993; ThermoFisher Scientific; Waltham MA)
Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 647 conjugate (1:1000; cat# A-21245; lot# 2018272; ThermoFisher Scientific; Waltham MA)
Goat anti-Rat IgG (H+L) Secondary Antibody, Alexa Fluor 647 conjugate (1:1000; cat# A-21247; lot# 536061; ThermoFisher Scientific; Waltham MA)
Goat anti-Chicken IgG (H+L) Secondary Antibody, Alexa Fluor 647 conjugate (1:1000, cat# A-21449; lot# 1932506; ThermoFisher Scientific; Waltham MA)

Validation

Antibodies were selected according to the antibody validation profiles reported by the distributing companies and in publications:
anti- CD68 (species, Rat): This antibody cited by 45 publications on manufacturer's website. We have also previously validated that this marker is specific to microglia in the CNS and decreasing or increasing phagocytic rates also modulates CD68 levels (Schafer et al. Neuron 2012) further demonstrating specificity of this marker for lyosomal proteins. (Smith and Koch, Journal of Cell Science 1987 original antibody source).
anti- VGluT2 (species, Guinea Pig): previously published work shows specificity for labeling thalamocortical inputs (Nahmani and Erisir J Comp Neurol 2005) and for use in detecting layer IV TC inputs in the barrel cortex (Hoshiko et al J. Neurosci 2012).
anti- Iba1 (species, Rabbit): The use of this antibody is cited by 68 publications on manufacturer's website. We have also validated it labels microglia and macrophages with co-labeling with other markers in our current study and past studies (Schafer et al. Neuron 2012; Schafer et al. eLife 2016).
anti- Homer1 (species, Rabbit): cited by 13 publications on manufacturer's website for specificity to Homer-1 protein.
anti- APP (species, Rabbit): appears in 40 published figures according to manufacturer's website including 24 references for use in IHC.
anti- Cleaved Caspase 3 (species, Rabbit): cited by 3,479 publications on manufacturer's website.
anti- ATF3 (species, Rabbit): cited by 13 publications on manufacturer's website (KO validated by Gey et al Open Biol. Royal Society 2019). Additionally, ATF3 reactivity was tested on dorsal root ganglion tissue following a sciatic nerve injury in collaboration with C. Woolf lab (Harvard Medical School). Increased ATF3 reactivity was observed in injured dorsal root ganglion tissue in accordance with previous published reports on ATF3 reactivity following injury.
anti- NeuN (species, chicken): NeuN (RNA binding protein fox-1 homolog 3; Fox-1 homolog C) is a RNA-binding protein found exclusively in the nuclei of neuronal cells. It is a member of the evolutionarily conserved Fox-1 family and is mainly involved in splicing of RNA. From manufacturer's website: This Anti-NeuN Antibody is validated for use in IHC(P), Western Blotting, ICC for the detection of NeuN.
anti- CD45 (species, Rat): cited by 19 references on manufacturer's website for specificity to CD45 protein.
anti- ALDH1L1 clone N103/39 (species, Mouse): From manufacturer's website: Anti-Aldh1L1, clone N103/39 is an antibody targeting the Aldh1L1 protein, validated for use in Immunofluorescence, Immunohistochemistry, and Western Blotting.
anti- NG2 (species, Rabbit): From manufacturer's website: NG2 Chondroitin Sulfate Proteoglycan. AB5320 identifies both the intact proteoglycan and the core protein by Western blot and ELISA. When oligodendrocyte precursor cells (i.e. O-2A progenitor cells) are stained alive, the stain appears as clusters on the cell surface. This antibody does not stain differentiated oligodendrocytes well.
anti- P2RY12 (species, Rabbit): From manufacturer's website: Each lot of this antibody is quality control tested by formalin-fixed paraffin-embedded immunohistochemical staining. For immunohistochemistry, a concentration range of 5.0 - 10 µg/ml is suggested. 1 publication cited on manufacturer's website.
anti- F4/80 (species, Rat): references by 29 publications according to manufacturer's website for specificity to F4/80. From website: MA1-91124 has been successfully used in immunohistochemistry (frozen tissue), immunohistochemistry (paraffin tissue), immunoprecipitation, Western blot, radioimmune assay and Flow cytometry applications.

Animals and other organisms

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

Laboratory animals

SERT-Cre mice were a generous gift from Dr. Mark Ansorage, Columbia University and provided by Dr. Sacha Nelson, Brandeis University. Cx3cl1-/- mice were provided by Dr. Sergio Lira (Ichan School of Medicine, Mount Sinai). Rosa26-TdTomato mice (Ai14; stock #007914), Cx3cr1-/- mice (Cx3cr1EGFP/EGFP; stock #005582), CR3-KO mice (stock #003991), and C57Bl6/J (stock #000664) mice were obtained from Jackson Laboratories (Bar Harbor, ME). Heterozygous breeder pairs were set up for all experiments and wild-type and heterozygote littermates were used as controls with equal representation of males and females for each genotype unless otherwise specified in figure legends. Mice were cauterized at postnatal day 4 (P4) for all whisker lesioning and whisker trimming experiments and sacrificed at various ages including P5, P6, P7, P8, P9, P10, P11, P21, and P90. See main text and figure legends for specific ages used in each experiment.

Wild animals

No wild animals were used in this study.

Field-collected samples

No field-collected samples were used in this study.

Ethics oversight	All experiments were performed in accordance with animal care and use committees (UMass Medical School IACUC) and under NIH guidelines for proper animal welfare.

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