

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

Top Scan Software version 3.00 was used to track and measure all behaviors.

Data analysis

GraphPad Prism 8 was used to represent data in graphs and for the statistical analyses of the data. The ImageJ software was used to outline and measure areas for imaging analysis.

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

Source Data for Figs. 1–4 and Extended Data Figs. 1, 3–7, and 9–10 containing raw data for all experiments, are provided with the paper. All other data 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](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	Sample size was chosen based on previous experiments and publications (5) (25), PMID:31482844, PMID:26311765.
Data exclusions	No data were excluded.
Replication	Key experiments were reiterated with representatives from each group with similar observations across iterations
Randomization	Subject animals were randomly assigned to experimental groups when applicable. Groups were determined based on genotype
Blinding	Investigators were blinded as to experimental groups during data collection and analysis.

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

Methods

n/a	Involvement in the study	n/a	Involvement in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies	<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines	<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology	<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Human research participants		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data		

Antibodies

Antibodies used	rat anti-GFAP (Invitrogen, 13-0300, Lot SA247423 1:500), mouse anti-calbindin (Sigma, C9848, Lot 058M4813V 1:1,000), rabbit anti-γH2AX (abcam, ab11174, Lot GR3280493-2 1:1,000), rabbit anti-53bp1 (abcam, ab21083, Lot GR3266130-1 1:1,000), Biotin conjugated NeuN (Millipore, MAB377B, Lot 3232375, 1:300)
Validation	These are all commonly used antibodies. Statements regarding validation can be found at the manufactures website.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals	Wild-type (WT) C57BL/6, Aim2 ^{-/-} , Casp1 ^{11/-} (Ice ^{-/-}) ³³ , Nr3 ^{-/-} , Myd88 ^{-/-} , Il1r ^{-/-} , Il18r ^{-/-} , R26-CAG-ASC-citrine5, Casp11 ^{-/-} , Casp1fl/fl39, NestinCre40, and Cx3cr1Cre41 mice were obtained from The Jackson Laboratory. Gsdmd ^{-/-} mice were generously provided by Vishva Dixit ⁴² . Mice were housed and behavior was conducted in specific pathogen-free conditions under standard 12hr light/dark cycle conditions in rooms equipped with control for temperature (21 ± 1.5oC) and humidity (50 ± 10%). For behavior, adult male (8-12 week old) were used, for postnatal day 5 (p5) experiments a mix of male and female mice were used.
Wild animals	Wild animals were not used in our studies.
Field-collected samples	Field-collected samples were not used in our studies.
Ethics oversight	All mouse experiments were performed in accordance with the relevant guidelines and regulations of the University of Virginia and approved by the University of Virginia Animal Care and Use Committee.

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