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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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	Latitude S 1.3 - commercially available, SerialEM 3.8 - published and freely available
Data analysis	Prism 7.0 and 10.0 - commercially available (GraphPad Software, Inc), pClamp 10.6 - commercially available (Molecular Devices), Igor Pro 6.2 - commercially available (WaveMetrics, Inc), Excel office 365 - commercially available (Microsoft), RELION 4.0 - published and freely available, UCSF pyem v0.5 - published and open source, CryoSPARC 4.0/4.1/4.4 - commercially available, Coot 0.9 - published and freely available, PHENIX 1.20 - published and freely available, UCSF Chimera X 1.6 - published and freely available, PyMOL 2.4.0 - open source

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](#)

The structure coordinates generated in this study have been deposited in the Protein Data Bank under accession codes 9ZYR [https://doi.org/10.2210/pdb9ZYR/pdb] (PIP₂-menthol-TRPM8 in C1M,4C state), 9PWE [https://doi.org/10.2210/pdb9PWE/pdb] (PIP₂-menthol-AITC-TRPM8 in C1M',4C state), 9PWF [https://

doi.org/10.2210/pdb9PWF/pdb] (PIP₂-menthol-TRPM8-I846V in C2M,20C state), 9PWG [https://doi.org/10.2210/pdb9PWG/pdb] (PIP₂-AITC-menthol-TRPM8-I846V in pre-OM,20C state), 9PWH [https://doi.org/10.2210/pdb9PWH/pdb] (PIP₂-AITC-TRPM8 in C1A,4C state), and 9Y69 [https://doi.org/10.2210/pdb9Y69/pdb] (PIP₂-AITC-menthol-TRPM8-I846V in C2M,4C state) and 9Y6A [https://doi.org/10.2210/pdb9Y6A/pdb] (PIP₂-AITC-menthol-TRPM8-I846V in OM,4C state). The corresponding cryo-EM maps generated in this study have been deposited in the Electron Microscopy Data Bank under the accession codes EMD-74963 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-74963] (PIP₂-menthol-TRPM8 in C1M,4C state), EMD-71916 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-71916] (PIP₂-menthol-AITC-TRPM8 in C1M',4C state), EMD-71917 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-71917] (PIP₂-menthol-TRPM8-I846V in C2M,20C state), EMD-71918 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-71918] (PIP₂-AITC-menthol-TRPM8-I846V in pre-OM,20C state), EMD-71919 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-71919] (PIP₂-AITC-TRPM8 in C1A,4C state), EMD-72557 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-72557] (PIP₂-AITC-menthol-TRPM8-I846V in C2M,4C state), and EMD-72558 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-72558] (PIP₂-AITC-menthol-TRPM8-I846V in OM,4C state).

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	NA
Reporting on race, ethnicity, or other socially relevant groupings	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

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 number of micrographs collected for cryo-EM structure determination was determined by sample quality and microscope time availability, with the goal of obtaining the resolution structure possible. For electrophysiology experiments, sample sizes of at least n=3 (biologically independent replicates) were sufficient to ensure reproducibility. Predetermination of sample size was not needed for the studies reported here and thus no sample size calculation was performed.
Data exclusions	No data were excluded from electrophysiology
Replication	At least triplicate (n ≥ 3) biological repeats were pursued for all functional experiments and were reproducible (sample size is noted in all cases in the figure legends).
Randomization	For electrophysiology experiments, we need to choose the best behave cell (least leak current, normal cell shape, etc) to record to minimize the background currents (leak currents).
Blinding	Blinding was not used for the functional and structural studies reported here since no grouping was performed.

Behavioural & social sciences study design

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

Study description	NA
Research sample	NA
Sampling strategy	NA
Data collection	NA

Timing	NA
Data exclusions	NA
Non-participation	NA
Randomization	NA

Ecological, evolutionary & environmental sciences study design

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

Study description	NA
Research sample	NA
Sampling strategy	NA
Data collection	NA
Timing and spatial scale	NA
Data exclusions	NA
Reproducibility	NA
Randomization	NA
Blinding	NA

Did the study involve field work? ☐ Yes ☒ No

Field work, collection and transport

Field conditions	NA
Location	NA
Access & import/export	NA
Disturbance	NA

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	A monoclonal mouse anti-FLAG M2 antibody (Sigma-Aldrich, F3165) was used at 1:1000x dilution and a polyclonal goat anti-mouse IgG HRP-conjugated (Rockland, 610-1302) was used at 1:10000x dilution.
Validation	From the manufacturer: Sensitivity Test Conforms: Detects 2 ng of FLAG-BAP fusion protein by dot blot using chemiluminescent detection. Specificity Confirmed: Detects a single band of protein on a western blot from an E. coli crude cell lysate.

Eukaryotic cell lines

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

Cell line source(s)	HEK293T cell were obtained from ATCC (CRL-11268).
Authentication	Cell lines were not authenticated.
Mycoplasma contamination	HEK293T cells were tested negative for mycoplasma contamination by Duke University Cell Culture Facility.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell line was used in this study.

Palaeontology and Archaeology

Specimen provenance	NA
Specimen deposition	NA
Dating methods	NA
☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.	
Ethics oversight	NA

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

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	NA
Wild animals	NA
Reporting on sex	NA
Field-collected samples	NA
Ethics oversight	NA

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

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	NA
Study protocol	NA
Data collection	NA
Outcomes	NA

Dual use research of concern

Policy information about [dual use research of concern](#)

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

- | No | Yes |
|-------------------------------------|---|
| ☒ | ☐ Public health |
| ☒ | ☐ National security |
| ☒ | ☐ Crops and/or livestock |
| ☒ | ☐ Ecosystems |
| ☒ | ☐ Any other significant area |

Experiments of concern

Does the work involve any of these experiments of concern:

- | No | Yes |
|-------------------------------------|--|
| ☒ | ☐ Demonstrate how to render a vaccine ineffective |
| ☒ | ☐ Confer resistance to therapeutically useful antibiotics or antiviral agents |
| ☒ | ☐ Enhance the virulence of a pathogen or render a nonpathogen virulent |
| ☒ | ☐ Increase transmissibility of a pathogen |
| ☒ | ☐ Alter the host range of a pathogen |
| ☒ | ☐ Enable evasion of diagnostic/detection modalities |
| ☒ | ☐ Enable the weaponization of a biological agent or toxin |
| ☒ | ☐ Any other potentially harmful combination of experiments and agents |

Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA

ChIP-seq

Data deposition

- ☐ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links May remain private before publication.	NA
Files in database submission	NA
Genome browser session (e.g. UCSC)	NA

Methodology

Replicates	NA
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Sequencing depth	NA
Antibodies	NA
Peak calling parameters	NA
Data quality	NA
Software	NA

Flow Cytometry

Plots

Confirm that:

- ☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☐ All plots are contour plots with outliers or pseudocolor plots.
- ☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	NA
Instrument	NA
Software	NA
Cell population abundance	NA
Gating strategy	NA

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	NA
Design specifications	NA
Behavioral performance measures	NA

Acquisition

Imaging type(s)	NA
Field strength	NA
Sequence & imaging parameters	NA
Area of acquisition	NA

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	NA
Normalization	NA
Normalization template	NA
Noise and artifact removal	NA
Volume censoring	NA

Statistical modeling & inference

Model type and settings	NA
Effect(s) tested	NA
Specify type of analysis:	☐ Whole brain ☐ ROI-based ☐ Both
Statistic type for inference	NA
(See Eklund et al. 2016)	
Correction	NA

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis