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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 Legion 3.5, EPU 2, PatchMater V2x69, pCLAMP 10.2

Data analysis RELION 4.0, cryoSPARC 3.3.2, UCSF ChimeraX 1.2, COOT 0.9.8.1, PHENIX 1.18, PyMOL 2.5.4, HOLE 2.1, GraphPad Prism 8.4.0, Clampfit 10.3, AmberTools 20, VMD 1.9.4, CHARMM-GUI 3.8

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 data needed to evaluate the conclusions in the paper are present in the paper and/or in the Supplementary Materials. Source data are provided with this paper. The cryo-EM maps have been deposited in the Electron Microscopy Data Bank with the following codes: EMD-40496 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40496>] (TRPM7closed in MSP2N2 nanodiscs), EMD-40497 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40497>] (TRPM7closed in GDN), EMD-40498 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40498>] (TRPM7-N1098Qopen), EMD-40499 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40499>] (TRPM7NTB-open), EMD-40500 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40500>] (TRPM7NTB-closed), EMD-40501 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40501>] (TRPM7VER-closed), EMD-40502 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40502>] (TRPM7-N1098QVER-closed), EMD-40504 [<https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40504>]

www.ebi.ac.uk/pdbe/entry/emdb/EMD-40504] (TRPM7-N1098QNS-closed), and EMD-40505 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-40505] (TRPM7 MHR1-3 domain). The coordinates for the atomic models have been deposited in the Protein Data Bank under accession codes 8SI2 [http://doi.org/10.2210/pdb8SI2/pdb] (TRPM7closed in MSP2N2 nanodiscs), 8SI3 [http://doi.org/10.2210/pdb8SI3/pdb] (TRPM7closed in GDN), 8SI4 [http://doi.org/10.2210/pdb8SI4/pdb] (TRPM7-N1098Qopen), 8SI5 [http://doi.org/10.2210/pdb8SI5/pdb] (TRPM7NTB-open), 8SI6 [http://doi.org/10.2210/pdb8SI6/pdb] (TRPM7NTB-closed), 8SI7 [http://doi.org/10.2210/pdb8SI7/pdb] (TRPM7VER-closed), 8SI8 [http://doi.org/10.2210/pdb8SI8/pdb] (TRPM7-N1098QVER-closed), 8SIA [http://doi.org/10.2210/pdb8SIA/pdb] (TRPM7-N1098QNS-closed), and 8SIB [http://doi.org/10.2210/pdb8SIB/pdb] (TRPM7 MHR1-3 domain). The core of the TRPM7Closed model was built using PDB structure 5ZX5 [http://doi.org/10.2210/pdb5ZX5/pdb] as a guide. All other data are available from the corresponding authors 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	Amount of cryo-EM data collected was limited by time allocation at the microscopes. For patch-clamp experiments and calcium influx assays, no sample size predetermination was performed. The reported sample size is based on accepted methodology and published works by us and others, and is sufficient to obtain reproducible and reliable data from patch-clamp experiments in HEK cells using TRPM channels
Data exclusions	No data has been excluded.
Replication	No replication attempts have failed. The cryo-EM data collection was consistent from the beginning to the end. A replication of the cryo-EM data collection was therefore not necessary or economically viable/justifiable. In calcium influx assays, patch-clamp experiments, and planar lipid bilayer recordings, we made at least three independent replicates for each construct.
Randomization	Samples were not randomized; it is not technically or practically feasible to do so for cryo-EM, calcium influx, patch-clamp or the conducted molecular dynamic simulation studies. Covariant control is not economically viable/justifiable in cryo-EM data collections or MD simulations. Covariant control was also not possible for calcium influx assays or patch-clamp studies due to the need to transfect with predetermined cDNAs and optimize protein expression for individual constructs.
Blinding	Researchers were not blinded; it is not technically or practically feasible to do so for cryo-EM, calcium influx assays, patch-clamp or the conducted molecular dynamic simulation studies. It is not economically viable/justifiable to blind cryo-EM collections or MD simulations. For calcium influx assays and patch-clamp studies, researchers conducting the studies were also in charge of cell as well as protein expression optimization for individual constructs in order to achieve recordings on transfected cells in these studies. These circumstances made blinding not possible.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)

HEK293 GnTI-, ATCC, Cat#CRL-1573
Sf9, Gibco, Cat#12659017
HEK 293T, ATCC, Cat#CRL-3216

Authentication

None of the cell lines used have been authenticated.

Mycoplasma contamination

The cell lines used have been tested for mycoplasma contamination by the providers (negative results) but have not been retested in the lab.

Commonly misidentified lines
(See [ICLAC](#) register)

No commonly misidentified lines were used in this study.