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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 EPU (Thermo Fisher Inc.), TILL Photonics /TILLvisION Ver 4.5.66

Data analysis cryoSPARC v4.9, Coot 0.9.5, ChimeraX 10, Phenix, Microsoft Excel, GraphPad Prism 8, Clampfit 9/10, AlphaFold3 (09/2025), FlexPepDock, OpenMM, Py_hole (github.com/mlbaker-uth/pyHole), Rosetta Energy_Breakdown, Clustal-omega, ESPript, Origin 6 software, Schrödinger Maestro

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](#)

Data supporting the findings of this manuscript are available from the corresponding author upon reasonable request. The cryo-EM maps have been deposited in the Electron Microscopy Data Bank (EMDB) under accession codes: EMD-76260 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76260] (Apo-IP3R2 consensus); EMD-76259 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76259] (Apo-IP3R2-composite); EMD-76249 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76249]

(Apo-IP3R2-local refinement of LBD); EMD-76250 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76250] (Apo-IP3R2-local refinement of ARM1-HD); EMD-76251 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76251] (Apo-IP3R2-local refinement of ARM2); EMD-76252 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76252] (Apo-IP3R2-local refinement of ARM3-ILD-LNK); EMD-76253 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76253] (Apo-IP3R2-local refinement of TMDs); EMD-76264 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76264] (CIA-IP3R2 consensus); EMD-76262 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76262] (CIA-IP3R2-composite); EMD-76254 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76254] (CIA-IP3R2-local refinement of LBD); EMD-76255 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76255] (CIA-IP3R2-local refinement of ARM1-HD); EMD-76257 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76257] (CIA-IP3R2-local refinement of ARM2); EMD-76258 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76258] (CIA-IP3R2-local refinement of ARM3-ILD-LNK); EMD-76256 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-76256] (CIA-IP3R2-local refinement of TMDs). Atomic coordinates have been deposited in the Protein Data Bank (PDB) under accession codes 12AD [https://doi.org/10.2210/pdb12AD/pdb] (Apo-IP3R2); 12AI, [https://doi.org/10.2210/pdb12AI/pdb] (CIA-IP3R2). Previously published structures used in this study: 7LHF [https://doi.org/10.2210/pdb7LHF/pdb] (Apo-IP3R1); 8EAR [https://doi.org/10.2210/pdb8EAR/pdb] (CIA-IP3R1); 7T3T [https://doi.org/10.2210/pdb7T3T/pdb] (CIA-IP3R3); 6DQJ [https://doi.org/10.2210/pdb6DQJ/pdb] (Apo-IP3R3).

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	See Table 1 and Supplementary Figs 1,2. Sample sizes were chosen based on established practices in the cryo-EM and ion channel fields, prior experience with similar experiments, and the amount of data required to obtain robust and reproducible results. For electrophysiological experiments, sample sizes were selected to provide adequate replication across independent recordings and to enable reliable statistical comparisons between experimental conditions. The chosen sample sizes were consistent with those commonly used and were sufficient to support reproducible and statistically robust conclusions.
Data exclusions	Iterative 2D and 3D classifications were used to eliminate particles.
Replication	Reproducibility of the final 3D maps was assessed using the gold-standard Fourier shell correlation 0.143 criterion. For cryo-EM, sufficient numbers of micrographs and particles were collected to achieve high-resolution reconstructions and to ensure consistency across independent refinements and analyses. Electrophysiological experiments were independently repeated. Consistent results were obtained across replicate recordings for each experimental condition.
Randomization	Randomization is implemented in image processing. Individual particle data sets were randomly split into odd and even halves and refined independently. For electrophysiological experiments, cells were assigned according to predefined expression constructs and treatment conditions required to test specific hypotheses. Because experimental groups were determined by experimental design no randomization procedure was performed. Standardized sample preparation, data acquisition, and analysis protocols were applied across all groups to minimize potential sources of variability and bias.
Blinding	Data was not blinded in cryoEM studies and electrophysiological experiments.

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	Involvement 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	Involvement in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Rabbit polyclonal antibody to mouse IP3R2 C-term peptide (last 19 residues) were produced commercially and 10-20 mg IgG utilized for immunoaffinity purification.
Validation	IP3R2 antibodies were validated by Western blot on cell lysates from 3KO cells expressing only IP3R2 gene. No additional validations were performed.

Eukaryotic cell lines

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

Cell line source(s)	HEK293S GNTI- (ATCC-CRL-3022), HEK293 (ATCC-CRL-3216), HEK-3KO (Kerafast-EUR030)
Authentication	cell lines were not authenticated
Mycoplasma contamination	GNTI- not tested for mycoplasma, HEK-3KO tested and negative
Commonly misidentified lines (See ICLAC register)	no

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A