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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 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 *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	Image Lab 6.1, MicroCal PEAQ-ITC v1.0, Quantstudio 6, SCIEX 1.6, Softmax Pro 7
Data analysis	autoPROC 20210224, BUSTER 2.11.7, CCP4 7.1.003, Coot 0.9.4.1, cryoSPARC v2.15, MotionCor2 v1.2.1, Phenix v1.19.2, Prism 8, Protein Thermal Shift v1.4, PyMOL 1.7.7.6, Refmac 5.8, SCIEX 1.6

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 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

The data generated or analyzed in the current study are available within the article, supplementary information, or from the corresponding authors upon reasonable request. Source data are provided with this paper. The structures reported in this work have been deposited in public repositories with the following accession codes: eIF2B-F6P cryo-EM structure: PDB 7KMF [http://doi.org/10.2210/pdb7KMF/pdb], EMDB EMD-22924 [https://www.ebi.ac.uk/pdbe/entry/emdb/EMD-22924]; eIF2B□-M6P X-ray crystal structure: PDB 7KMA [http://doi.org/10.2210/pdb7KMA/pdb].

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	Sample size calculations were not performed. Sample sizes were chosen based on pilot experiments and experimental limitations. Data variance was sufficiently low in all in vitro experiments that sample sizes did not constrain analysis.
Data exclusions	No data were excluded from analysis.
Replication	Biological (n=2-4) and technical (n=2-3) replicates were used for experiments. All replicates behaved similarly.
Randomization	Randomization was not performed. All samples were generated de novo for each experiment.
Blinding	Experiments were not blinded. Data analysis was performed in an unbiased fashion by applying the same analysis parameters to each sample in an experiment.

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

Antibodies

Antibodies used	eIF2B1 (Proteintech #18010-1-AP, polyclonal); eIF2B4 (Proteintech #11332-1-AP, polyclonal); eIF2B5 (Bethyl Labs #A302-556, polyclonal); eIF3a (Cell Signaling Technology #3411, clone D51F4); eIF2S1 (Cell Signaling #5324, clone D7D3); p-eIF2S1(Ser51) (Cell Signaling #3398, clone D9G8); FLAG (Sigma #F1804, clone M2)
Validation	All antibodies validated by manufacturers for Western Blots on human proteins

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Generated in-house from ATCC parental HEK293T cell line
Authentication	ATCC STR profiling
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study