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.

☑ 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. t, F, r) with confidence intervals, effect sizes, degrees of freedom and P value noted. Give P values as exact values wherever possible.
☒ 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

GazeMovie software (Version 1.7.7, CerebralMechanics Inc., Lethbridge, Alberta, Canada) was used for optokinetic tracking response collection purposes. Velocity software (Cembran Technologies) was used for ROPMS – RGCs counting purposes.

Data analysis

GraphPad Prism 7 was used to generate graphs and for statistical analyses. ImageJ (1.8.0) was used for quantification analyses. Analyst software 1.6.2 (Scien) was used for calibration curve fitted by linear regression. The average thickness of GCC around the ON head was measured manually with the aid of Heidelberg software.

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, and researchers. 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

A reporting summary for this article is available as Supplementary Information file. The main data supporting the findings of this study are available within the article and its Supplementary Figures. The source data underlying Figs. 1–8 and Supplementary Figs. 1–9 are provided as a Source data file. Specific data deposition values are also included within the Source Data file. Additional details on data sets and protocols that support the findings of this study will be made available by the corresponding author upon reasonable request. Source data are provided with this paper.
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 sizes were chosen based on previous experience and were indicated in the legend of each Figure and Supplementary Figure. No statistical methods were used to predetermine sample sizes. Experiments were reliably reproduced using independent samples. Data are provided as a source data file. References: 1, Neuron. 2022 Aug 17;110(16):2646-2663.e6. doi: 10.1016/j.neuron.2022.06.022. 2, Mol Ther. 2022 Apr 6;30(4):1421-1431. doi: 10.1016/j.ymthe.2022.01.035. 3, Nat Cell Biol. 2022 Apr;24(4):590-600. doi: 10.1038/s41556-022-00870-7. 4, Nat Commun. 2019 Sep 20;10(1):4303. |
| Data exclusions | The elimination criteria of outliers were based on the visible health status of the individual mice. The mice underwent significant weight loss or appearing sick were excluded from data analysis. |
| Replication | All laboratory analyses were conducted in duplicate technical replicates. All data were obtained from independent biological replicates as described in the figure legends. |
| Randomization | For cell based experiments in vitro seeded cell populations were randomly allocated to treatment groups prior to treatment. All mice were randomly allocated into experimental groups before the start of the treatment. Important findings were repeated with independent experiments. |
| Blinding | Investigators were blinded to group allocation. For observer-based microscopy data assessment and collection, observers were masked to the treatment of the samples. For in vivo SLO, PERG, OKR and SD-OCT recording, the data collection was undertaken in a double blinded fashion, with observers unaware of treatment groupings or prior determined measurements. Key experiments were validated in independent experiments. Selected data was analyzed by different investigators to validate findings. |

Behavioural & social sciences study design

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

| Study description | Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study). |
| Research sample | State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source. |
| Sampling strategy | Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed. |
| Data collection | Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection. |
| Timing | Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort. |
| Data exclusions | If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established. |
| Non-participation | State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation. |
| Randomization | If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled. |
### Ecological, evolutionary & environmental sciences study design

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

#### Study description
Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.

#### Research sample
Describe the research sample (e.g. a group of tagged Passer domesticus, all Stenocereus thurberi within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.

#### Sampling strategy
Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.

#### Data collection
Describe the data collection procedure, including who recorded the data and how.

#### Timing and spatial scale
Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken.

#### Data exclusions
If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.

#### Reproducibility
Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.

#### Randomization
Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.

#### Blinding
Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.

#### Field work, collection and transport

##### Field conditions
Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).

##### Location
State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).

##### Access & import/export
Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information).

##### Disturbance
Describe any disturbance caused by the study and how it was minimized.

### 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

| Involved in the study | n/a | Antibodies | Eukaryotic cell lines | Palaeontology and archaeology | Animals and other organisms | Human research participants | Clinical data | Dual use research of concern |
|-----------------------|-----|-------------|-----------------------|-------------------------------|-----------------------------|-----------------------------|--------------|-----------------------------|
|                       |     | x           | x                     |                               | x                           |                             |              |                             |

#### Methods

| Involved in the study | n/a | ChIP-seq | Flow cytometry | MRI-based neuroimaging |
|-----------------------|-----|----------|----------------|-------------------------|
|                       |     | x        | x              | x                       |
Antibodies

The primary antibodies used were PERK (Cell Signaling, 3192S), p-PERK (Cell Signaling, 3179S), eIF2α (Cell Signaling, 5324S), p-eIF2α (Cell Signaling, 3597L), ATF4 (Cell Signaling, 11815S), CHOP (Cell Signaling, 2895S), ATF6 (Cell Signaling, 65807T), IRE1α (Cell Signaling, 3294T), IRE1 (phospho-S724) (Thermofisher, PA116927), phospho-SAPK/JNK (Thr183/Tyr185) (Cell Signaling, 9251S), phospho-p38 MAPK (Thr180/Tyr182) (Cell Signaling, 9251S), β-Actin (sigma, A5441), XBP-1s (Biolegend, 647502), HRH1 (Thermofisher, 13413-1-AP), peroxidase-conjugated secondary antibodies (Cell Signaling, 7074s and 7076s). The dilution used for each antibody has mentioned in the methods section of this literature.

Only highly cited and thoroughly validated antibodies were chosen and used. All primary antibodies used in this study work well for immunoblotting and immunohistochemistry in human or mouse samples. The expression pattern for each antibody matches previous reports in the literature.

Eukaryotic cell lines

HEK293T was obtained from ATCC (CRL-11268).

The cell line used was not authenticated.

HEK293T was tested negative for mycoplasma.

No commonly misidentified cell lines were used in this study.

Palaeontology and Archaeology

Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information).

Indicate where the specimens have been deposited to permit free access by other researchers.

If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

Animals and other organisms

C57BL/6J WT (#000664) mice (7-9 weeks old, male) were purchased from Jackson Laboratories (Bar Harbor, Maine) and housed in standard cages on a 12-hour light–dark cycle, with room temperature at 25±2°C and humidity between 40 and 60%.

This study did not involve samples collected from the field.

All experimental procedures were performed in compliance with animal protocols (#32093) approved by the IACUC at Stanford University School of Medicine.

Human research participants

Describe the covariate-relevant population characteristics of the human research participants (e.g. age, gender, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."

Describe how participants were recruited. Outline any potential selection bias or other biases that may be present and how these are likely to impact results.
Ethics oversight

Identify the organization(s) that approved the study protocol.

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

Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.

### Study protocol

Note where the full trial protocol can be accessed OR if not available, explain why.

### Data collection

Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.

### Outcomes

Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.

## 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 |
| ![x] | ![ ] | National security |
| ![x] | ![ ] | Crops and/or livestock |
| ![x] | ![ ] | Ecosystems |
| ![x] | ![ ] | Any other significant area |

### Experiments of concern

Does the work involve any of these experiments of concern:

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

## 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

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

### Files in database submission

Provide a list of all files available in the database submission.

### Genome browser session (e.g. UCSC)

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.
## Methodology

### Replicates
Describe the experimental replicates, specifying number, type and replicate agreement.

### Sequencing depth
Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

### Antibodies
Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

### Peak calling parameters
Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

### Data quality
Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

### Software
Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

## 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
Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.

#### Instrument
Identify the instrument used for data collection, specifying make and model number.

#### Software
Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.

#### Cell population abundance
Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

#### Gating strategy
Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.

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
Indicate task or resting state; event-related or block design.

#### Design specifications
Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

#### Behavioral performance measures
State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).
## Acquisition

| Imaging type(s)                     | Specify: functional, structural, diffusion, perfusion. |
|------------------------------------|--------------------------------------------------------|
| Field strength                     | Specify in Tesla                                      |
| Sequence & imaging parameters      | Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle. |
| Area of acquisition                | State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined. |
| Diffusion MRI                      | □ Used □ Not used                                      |

## Preprocessing

| Preprocessing software             | Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.). |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Normalization                      | If data were normalized/standardized, describe the approach(es); specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization. |
| Normalization template             | Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MN105, ICBM152) OR indicate that the data were not normalized. |
| Noise and artifact removal         | Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration). |
| Volume censoring                   | Define your software and/or method and criteria for volume censoring, and state the extent of such censoring. |

## Statistical modeling & inference

| Model type and settings            | Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation). |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Effect(s) tested                   | Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used. |
| Specify type of analysis: □ Whole brain □ ROI-based □ Both | Specify the type of analysis and whether it is voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods. |
| Statistical type for inference     | Specify the type of inference and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo). |

## Models & analysis

| Models & analysis                  | Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information). |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Functional and/or effective connectivity | Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject or group level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.). |
| Multivariate modeling and predictive analysis | Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics. |