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
  
  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: n/a

Data analysis: n/a

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

n/a
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 https://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  | 4-5 |
|--------------|-----|
| Data exclusions | none |
| Replication | 4-6 in duplicates |
| Randomization | Animals were assigned to groups randomly before testing |
| Blinding | n/a |

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: The phosphosite-specific MOP antibodies against pT370-MOP (7TM0319B), pS375-MOP (7TM0319C), pT376-MOP (7TM0319D), and pT379-MOP (7TM0319E); the phosphosite-specific CSa1 antibodies against pT326/pS327-CSa1 (7TM0032A), pS332/pS334-CSa1 (7TM0032B), and pS338/pT339-CSa1 (7TM0032D); and phosphosite-specific D1 dopamine receptor antibodies against pT354-D1 (7TM0214A) and pS372/pS373-D1 (7TM0214B), and phosphosite-specific SS2 antibodies against pS341/pS343-SS2 (7TM0356A) and pT356/pT359-SS2 (7TM0356C); and phosphosite-specific CB2 cannabinoid receptor antibodies pS335/pS336-CB2 (7TM0057A) and pS338/pS340-CB2 (7TM0057B); as well as the phosphorylation-independent antibodies against np-MOP (7TM0319N), np-CSa1 (7TM0032N), np-SS2 (7TM0356N), and rabbit polyclonal anti-IAA antibodies (7TM0000A) were provided by 7TM Antibodies (Iena, Germany). Phosphosite-specific antibodies were affinity-purified against their immunizing phosphorylated peptides and subsequently cross-adsorbed against the corresponding unphosphorylated peptides. All phosphosite-specific antibodies have been extensively characterized using western blot and dot blot analyses before application in 7TM phosphorylation assays7, 16, 19, 20, 21, 22, 34, 35, 46, 47, 48, 49 [Supplementary Figure 9 and 10] (www.7tammbodies.com).

**Validation**

Phosphosite-specific antibodies were affinity-purified against their immunizing phosphorylated peptides and subsequently cross-adsorbed against the corresponding unphosphorylated peptides. All phosphosite-specific antibodies have been extensively characterized using western blot and dot blot analyses before application in 7TM phosphorylation assays7, 16, 19, 20, 21, 22, 34, 35, 46, 47, 48, 49 [Supplementary Figure 9 and 10] (www.7tammbodies.com).

**Eukaryotic cell lines**

Policy information about cell lines

**Cell line source(s)**

- HEK293 cells were originally obtained from DSMZ Germany (ACC 305).

**Authentication**

- HEK293 cells were originally obtained from DSMZ Germany (ACC 305).
Mycoplasma contamination
Cells were passaged every 3–4 days and regularly checked for mycoplasma infections using a GoTaq G2 Hot Start Taq Polymerase kit from Promega.

Commonly misidentified lines
(See ICLAC register)
Name any commonly misidentified cell lines used in the study and provide a rationale for their use.

Animals and other organisms
Policy information about studies involving animals: ARRIVE guidelines recommended for reporting animal research

Laboratory animals
For in vivo phosphorylation experiments, knock-in mice expressing HA-MOP (Oprm1em1Shiz, MGI:6117675) were treated and brain lysates were prepared as described.

Wild animals
Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.

Field-collected samples
For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.

Ethics oversight
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.

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