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☐ Initial submission ☒ Revised version ☐ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.	No statistical methods were used to predetermine sample size.

2. Data exclusions

Describe any data exclusions.	Data were excluded only in experiments where viral injections were performed and post-hoc analysis of viral targeting demonstrated that injections were inaccurate.

3. Replication

Describe whether the experimental findings were reliably reproduced.	Results described throughout the paper were reproduced. Multiple rounds of experimentation were required, and multiple methods were used where applicable (e.g., multiple drugs of abuse show similar increases in rabies-labeled GPe inputs, Extended Data Fig. 1, and multiple methods of GPe inhibition all block LMS and CPP, Fig. 4). No issues were identified in replicating any of the reported findings.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.	Experiments described in Fig.'s 1, 2a-h and 2l-n, 3, 5g-j and Extended Data Figs. 1a, 4, 5, 6, 8, and 10 were randomized and investigators were blinded to allocation and outcome assessments; all other experiments were not randomized and investigators were not blinded.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.	Experiments described in Fig.'s 1, 2a-h and 2l-n, 3, 5g-j and Extended Data Figs. 1a, 4, 5, 6, 8, and 10 were randomized and investigators were blinded to allocation and outcome assessments; all other experiments were not randomized and investigators were not blinded.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	MATLAB software was used to analyze fiber photometry data All electrophysiology data were collected using Axograph software. GraphPad Prism was used to analyze all other data.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	There are no restrictions on materials.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	The following primary antibodies were used: Rat anti-mCherry, Life Sciences, 1:2000; chicken anti-GFP, Aves Labs, 1:1000; rabbit anti-TH, Millipore, 1:1000; Goat anti-Fos, Santa Cruz, 1:500. The following secondary antibodies were used from Jackson ImmunoResearch at a concentration of 1:250: donkey anti-chicken AlexaFluor488; donkey anti-goat AlexaFluor488; donkey anti-rat AlexaFluor555; donkey anti-goat AlexaFluor555; donkey anti-rabbit AlexaFluor647. Antibodies were validated 1. In the case of an extensively published antibody, by testing the specificity of staining to the appropriate regions (e.g. tyrosine hydroxylase, TH), or 2. by comparing between animals (e.g. cFos) and noting labeling that is above background but not consistent with non-specific staining.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used. N/A

b. Describe the method of cell line authentication used. N/A

c. Report whether the cell lines were tested for mycoplasma contamination. N/A

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use. N/A

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

Mice were housed on a 12-hour light/dark cycle with food and water ad libitum. Males and females from a mixed CD1 and C57/BL6 background were used for all experiments in approximately equal proportions. All surgeries were done under isoflurane anesthesia. All procedures complied with the animal care standards set forth by the National Institute of Health and were approved by Stanford University's Administrative Panel on Laboratory Animal Care and Administrative Panel of Biosafety.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

N/A