

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 (<i>n</i>) 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> 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 <i>d</i> , Pearson's <i>r</i>), 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	Two-photon images were acquired using Prairie View (Bruker, v5.7) software. Continuous food intake and energy expenditure measurements were collected using PhenoMaster 's (TSE, v5.0.6) or Promethion's (Sable, v23.0.01) custom software. Orofacial taste reactivity videos were analyzed using iMovie (v10.2.2). Real-time place avoidance data were acquired with EthoVision XT 16 (Noldus) software.
Data analysis	Python (v3.11.6), Prism (v.10.2.2), and Seurat (v.4.3.0) in R (v.4.3.0) software were used for data and statistical analyses. Python packages included CalmAn (v1.9.16), NoRMCorre (v0.1.1), Cellpose (v2.0.5), PyStackReg (v0.2.7). ggplot2 (v3.5.0) was used for transcriptomics analyses. Custom codes are available at https://github.com/alhadefflab/2p_imaging_analysis .

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](#)

Source data are provided with this paper.

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender

Population characteristics

Recruitment

Ethics oversight

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	Power analyses were run [beta = 0.2 (80% power), alpha =0.05] with effect sizes based on pilot studies (n=3-6) to ensure that sample sizes (number of mice for behavioural studies, number of neurons for physiological/anatomical studies) were sufficient to determine significant differences between groups. Based on these results, we repeated experiments in an additional cohort (or cohorts) of mice. For neural imaging we used 5-7 mice, and for anatomical experiments (comparing proportions of neurons), we analyzed 3 brain sections per mouse from at least 3 mice per group, which are standard sample sizes for imaging and anatomical studies in the neuroscience field.
Data exclusions	There were no exclusions from the data except for the following: For food intake measurements, mice with significant spillage were excluded from analysis (n=3 from DVC NaChBac studies, n=5 from Casp3/DTA/control ablation studies, and n=3 from GLP1R deletion studies). For neural ablation experiments (across several cohorts of 5 experimental groups of mice), n=4 mice were excluded because of unexpected illness and euthanasia during experimentation. For meal pattern analyses, mice with no food intake were excluded from inter-meal interval analyses (n=2 mice in APGLP1R vs. NTSGLP1R chemogenetic stimulation experiments). Across all taste reactivity experiments, n=1 mouse was excluded for a strong aversive response at baseline. For real-time place avoidance studies, n=3 data points were excluded due to mice escaping the apparatus. Where appropriate, viral expression was verified post-mortem; any mouse that did not express virus or expressed virus outside of the target region was excluded from analyses.
Replication	All behavioural experiments were performed in at least two cohorts, and data were combined and analyzed together, to ensure replicability of findings. For imaging experiments, we used at least 5 biological replicates per experimental condition. For histology experiments, we used at least 3 biological replicates per experimental condition. All attempts at replication were successful.
Randomization	Male and female mice were randomly allocated into experimental groups, ensuring that each sex was approximately equally represented in each group. For experiments involving diet-induced obesity, groups were pseudo-randomly generated to ensure that both groups were matched for body weight.
Blinding	Investigators collecting (e.g., performing behavioural measurements) or analyzing (e.g., counting neurons) data were blinded to experimental conditions.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	sheep anti-EGFP (1:1000, 4745-1051, Lot 1710, Bio-Rad) rabbit anti-RFP (1:1000, 600-401-379, Lot 46510, Rockland) donkey anti-sheep IgG Alex488 (1:500, 713-545-147, Lot 146368, Jackson ImmunoResearch) donkey anti-rabbit IgG Cy3 (1:500, 711-165-152, Jackson, Lot 145930, ImmunoResearch)
Validation	Primary antibodies were used to amplify virally-expressed fluorophore expression and have been validated in previous publications. Information on validation and citations can be found: For sheep anti-EGFP (92 citations): https://www.citeab.com/antibodies/111142-4745-1051-sheep-anti-green-fluorescent-protein?des=a92c6b1c71f0385b For rabbit anti-RFP (1129 citations): https://www.citeab.com/antibodies/1908633-600-401-379-anti-rfp-rabbit-antibody-min-x-hu-ms-a?des=0ec4a501cc3935ee

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	Adult (>8 weeks old) male and female Glp1r-IRES-Cre (029283, Glp1rtm1.1(cre)Lbrl/RcngJ, Jackson Labs), Ai9 (007909, B6.Cg-Gt(ROSA)26Sortm9(CAG-tdTomato)Hze/J, Jackson Labs), Glp1rtm1Ssis (Glp1rfl/fl, MGI:5637837, a gift from Randy Seeley), and C57BL/6J (000664, Jackson Labs) mice were bred and used for all experiments. Mice were group housed (maximum of 5 mice/cage) on a 12 h light/12 h dark cycle at 22°C with ad libitum access to rodent chow (5001, LabDiet) and water unless otherwise noted in the manuscript. Humidity was maintained on average at 55%.
Wild animals	The study did not involve wild animals.
Reporting on sex	Sex was determined at weaning by ano-genital distance and confirmed again prior to experimentation. Male and female mice were used for experimentation, except for one experiment (Fig. 1e) where only males were used to avoid the confounding variable of time post-neural ablation, because our female mice did not achieve diet-induced obesity with 8 weeks of high-fat diet exposure. Except for one experiment (Extended Data Fig. 1f) which had a smaller but still significant effect in female compared to male mice, we did not observe any significant sex differences in any analyses and therefore we combined results for males and females.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All procedures were approved by the Monell Chemical Senses Center Institutional Animal Care and Use Committee.

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