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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	For locomotor activies, ANY-maze software (v_7.08) was used for data collection. For image acquisition, LASX software (v_3.7.4) was used. For metabolic activities in mice PhenoMaster TSE Systems Inc software was used. For fiber photometry, Synapse Tucker-Davis Technologies software was used. For mice feeding patter, Graphic state (v_4) was used.
Data analysis	For position tracking and general locomotor activities were analyzed with ANY-maze software (v_7.08 Stoelting). For fiber photometry analysis, custom Matlab (v_2016a) scripts derived from Lerner et al. 2016 were used and will be made available for public access. For image analysis, ImageJ NIH (v_1.50g, v_1.52a) was used. For 10x Genomics sequencing, CellRanger (v_3.1.0) and Seurat (v_3.2) were used. For fMRI analyses, Statistical Parametric Mapping v12 (SPM12) and custom routines in MATLAB (v_2016a) were used. For statistics of mice data, GraphPad Prism (v_7 & 8) were used.

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

The sequencing datasets generated in this study are accessible at Gene Expression Omnibus under accession GSE184385 This manuscript contains all other

datasets except the processed sequencing data, raw fibre photometry datasets and codes for analysis which have been uploaded to Mendeley Data. http://dx.doi.org/10.17632/d82xx5ybs2.1

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	Power analyses were performed based on predicted effect sizes for each experiment based on pilot studies in the lab and effect sizes reported in published studies by us and others.
Data exclusions	Mice with fiber optic off-target positioning for dopamine sensing and calcium activity recording experiments (data not shown), and statistical outlier (Extended data 4j - one data point from aDCN-LAT) were excluded.
Replication	Gene expression, behavioral, neural activity and dopamine activity experiments were replicated at least twice and were successful. Performed by 2 different researchers that were blinded to condition.
Randomization	Animals were randomly organized into experimental groups, using counter-balanced experimental approaches wherever necessary during the conduct & data collection. For post-mortem histology and gene expression experiments, brain tissues were mounted on same slide in a counter-balanced manner. Imaged data was randomized by researcher A for researcher B to conduct analyses.
Blinding	For behavioral assays, and neuronal activity/dopamine efflux recordings the experimenter(s) was(were) blinded during data collection (conduct of recordings and behavioral assays). For neuron quantification and gene expression analyses, researcher(s) was(were) blinded to data analysis (blinded to data).

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	Primary antibodies, guinea pig anti-tdTomato (1:20000; Abcam Custom preparation; Betley et al., 2013 (doi:10.1016/j.cell.2013.11.002)), rabbit anti-GFP (1:1000; Invitrogen, A-11122), mouse anti-tyrosine hydroxylase (1:500; Chemicon, AB152), mouse anti-SMI 32 (1:1000; Biolegend, SMI-32P), guinea pig anti-vGluT2 polyclonal antibody (1:1000; Sigma-Aldrich, AB2251-I). Secondary antibodies Cy™3, Alexa Fluor®488 and rCy™5-conjugated donkey anti-guinea pig, -rabbit and -mouse (1:500; Jackson ImmunoResearch)
Validation	Guinea pig anti-tdTomato: Betley et al., 2013 (doi:10.1016/j.cell.2013.11.002). Rabbit anti-GFP: https://www.thermofisher.com/antibody/product/GFP-Antibody-Polyclonal/A-11122 (Relative expression validated) Mouse anti-tyrosine hydroxylase: https://www.sigmaaldrich.com/US/en/product/mm/ab152 (validated expression in brain). Mouse anti-SMI 32: https://www.biolegend.com/en-us/products/purified-anti-neurofilament-h-nf-h-nonphosphorylated-antibody-11475?GroupID=BLG15643 (WB & IHC-P quality validated; see also, Low et al., 2018 doi.org/10.1016/j.celrep.2018.02.017). Guina pig anti-vGluT2: https://www.emdmillipore.com/CA/en/product/Anti-Vesicular-Glutamate-Transporter-2-Antibody,MM_NF-MAB5504 (WB & IHC validated with certification; See also, Low et al., 2018 doi.org/10.1016/j.celrep.2018.02.017) Secondary antibodies validated: immunoaffinity chromatography purified, immunoelectrophoresis and/or ELISA antibody specificity tested. Cy™3 AffiniPure Donkey Anti-Guinea Pig IgG (H+L) https://www.jacksonimmuno.com/catalog/products/706-165-148. AffiniPure Donkey Anti-Guinea Pig IgG (H+L) https://www.jacksonimmuno.com/catalog/products/706-545-148. Alexa Fluor® 488 AffiniPure Donkey Anti-Rabbit IgG (H+L) https://www.jacksonimmuno.com/catalog/products/711-545-152. Alexa Fluor® 488 AffiniPure Donkey Anti-Mouse IgG (H+L) https://www.jacksonimmuno.com/catalog/products/715-545-150 Cy™5 AffiniPure Donkey Anti-Mouse IgG (H+L) https://www.jacksonimmuno.com/catalog/products/715-175-150

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Adult C57BL/6J, vGluT2-IRES-Cre (Slc17a6tm2(cre)Lowl/J), DAT-IRES-Cre (B6.SJLSlc6atm1.1(cre)Bkmn/J)10, TRAP2 (Fostm2.1(icre/ERT2)Luo/J), Ai9 (B6.Cg-Gt(ROSA)26Sortm9(CAG-tdTomato)Hze/J), vGluT2-Cre (Tg(Slc17a6-icre)1Oki)14, Ai32 (B6.Cg-Gt(ROSA)26Sortm32(CAG-COP4*H134R/EYFP)Hze/J), Agrp-IRES-Cre (Agrptm1(cre)Lowl/J), mice were 8-10 weeks old at the start of all experiments. Both male and female mice were used in all experiments. Mice were kept under a 12 hour light/dark cycle, animal biosafety level 1 laboratory conditions, with controlled temperature of 21.5 to 22.3 degree Celsius, humidity 50±15%, and negative pressured rooms (-191.6 to 109.5 Pascal).

Wild animals	Study did not involve wild animals.
Field-collected samples	Study did not involve field-collected samples.
Ethics oversight	All mice procedures were approved by and conducted in accordance with the ethical guidelines of the Nanyang Technology University Singapore and the University of Pennsylvania Institutional Animal Care and Use Committee (NTU #151069, Penn #805793).

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Data were collected from individuals with Prader-Willi syndrome (PWS) [n=14; 12 F/2 M; 2 Type 1 Deletion, 8 Type 2 Deletion, 4 uniparental disomy; mean age (years)=24.3±11.3; mean BMI (kg/m2) =32.1±7.8] and controls, individuals with simple obesity (OB group; n=14; 9 F/5 M; mean age=25.0±10.3; mean BMI=32.4±3.5). Groups were matched on sex (Fisher's Exact Test significance=0.39), age (t(26)=0.18, n.s.), BMI (t(26)=0.14, n.s.), and handedness (all right-handed). Diagnosis of PWS was confirmed through chromosomal and DNA molecular analysis as previously described. Concomitant psychotropic medications in the PWS group included (number of subjects): buspirone (1), clonazepam (1), divalproex (2), escitalopram (1), fluoxetine (1), fluvoxamine (1), lorazepam (1), quetiapine (1), risperidone (1), topiramate (1), sertraline (1), and ziprasidone (1). One PWS participant was being treated for hypothyroidism. Seven PWS subjects and all OB subjects were medication-free. All participants were free from current growth hormone treatment, history of appetite suppressant use, and history of neurological illness. All participants were free from current growth hormone treatment, history of appetite suppressant use, and history of neurological illness.
Recruitment	Participants in this study were volunteers recruited locally and nationally through the PWS Association (USA) website and the PWS-USA annual conference. There is unlikely any self-selection bias or influence of subjective reporting of symptoms since the disorder is a genetic lesion and thus defined objectively.
Ethics oversight	Human study was approved by the Human Subjects Committees at the University of Kansas (KUMC) and University of Rochester (URMC) Medical Centers. Written informed consent was obtained from parents and assent was obtained from participants.

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

Magnetic resonance imaging

Experimental design

Design type	Food cue paradigm using a block design
Design specifications	A total of two 6.5-minute runs following a block design (2.5 sec/image + 0.5 sec interstimulus interval; 10 images/block; 13 blocks/run) were presented.
Behavioral performance measures	A recognition memory task was performed post-scan to ensure participants were attending to stimuli. From each of the food and animal groups, ~50% of the images used in the scanning session (30 images) were chosen for recall (old) and interspersed with 15 novel distracter images from the same category (new). Participants completed a recognition memory task outside the scanner, immediately after each scanning session. Participants were instructed to press one key if they had seen the image in the scanner (old) and another key if they had not seen the image (new). Because of our small sample size (n=14 for PWS, n=14 controls), we used A' statistics, a non-parametric equivalent of d'. Mean A' values were computed for food and non-food items in the pre- and post-meal condition within each group. Wilcoxon signed rank tests were used to compare observed performance to chance (i.e., 50% correct). Both groups performed better than chance ($Z>2.37$, $p<0.01$) for both pre- and post-meal sessions.

Acquisition

Imaging type(s)	Functional MRI
Field strength	3 Tesla
Sequence & imaging parameters	At each scanning session (pre-meal and post-meal), one anatomical and two functional sequences were collected. T1-weighted anatomical images were acquired using similar 3D MP-RAGE sequences at each site [KUMC: coronal, repetition time/echo time (TR/TE)=23/4 ms, flip angle=8°, field of view (FOV)=256x192 mm, slice thickness=1 mm; URMC: sagittal, TR/TE=20/4 ms, flip angle=15°, FOV=256x256 mm, slice thickness=1 mm]. Single shot gradient echo planar imaging (EPI) fMRI scans were also acquired at each site using similar sequences (KUMC: 43 contiguous coronal slices, TR/TE=3000/40 ms, flip angle=90°, FOV=192x192 mm, slice thickness=3 mm, in-plane resolution=3x3 mm, 130 data points; URMC: 43 contiguous coronal slices, TR/TE=3000/36 ms, flip angle=90°, FOV=192x192 mm, slice thickness=3 mm, in-plane resolution=3x3 mm, 130 data points). A shorter TE (36 vs. 40 ms) at the URMC site provided ~7% higher signal-to-noise ratio (SNR) based on the typical T2* in cortical gray matter7, but ~10% lower task-induced BOLD signal change. Because the fMRI contrast-to-noise ratio (CNR) is proportional to the product of SNR and BOLD signal changes, we estimated ~3% CNR at TE = 36 ms. Therefore, it was expected that the overall effect of the TE difference was not significant and within the range of the experimental variations. Moreover, given the rarity of PWS

and the need for larger samples, the compromise of slightly different acquisitions was justified.

Area of acquisition: Whole brain acquisition was used.

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: fMRI data were pre-processed using Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging) and custom routines in MATLAB (Mathworks, Inc.). Volumes were realigned and corrected for bulk-head motion, normalized, resampled at 3 mm isotropic, and smoothed with a 6 mm Gaussian filter kernel.

Normalization: Volumes were normalized to the Montreal Neurological Institute (MNI) MNI152 brain template using trilinear interpolation.

Normalization template: Montreal Neurological Institute (MNI) MNI152 brain template

Noise and artifact removal: Outliers in the global mean image time series (threshold: 3.5 S.D.) and motion (threshold: 3.8mm translational movement or 0.05 radians rotational movement) were detected using the Artifact Detection Toolbox (http://www.nitrc.org/projects/artifact_detect/).

Volume censoring: Volumes corresponding to the outliers in the global mean image time series and motion (defined above) were censored using nuisance regressors in the first-level general linear model.

Statistical modeling & inference

Model type and settings: First-level models were statistical analysis was performed at the single (first) level. SPM treats each voxel's BOLD time series according to a general linear model. Each epoch of trials was modelled using a boxcar function convolved with a canonical hemodynamic response function. The contrast of interest (food versus non-food) from the single-subject analysis was tested using linear contrasts, and SPM t-maps, then submitted to second-level random effects group analysis.

Effect(s) tested: At the second (group) level, a random effects, full factorial ANOVA model was specified for the primary contrast of interest (food vs. non-food) to examine the Group (PWS, OB) x Session (pre-meal, post-meal) interaction at the whole-brain level.

Specify type of analysis: ☒ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016): Cluster-wise inference was used. We report clusters that (a) were significant at p<0.01 uncorrected and (b) exceeded an extent threshold of k=50.

Correction: We report clusters that were uncorrected for multiple comparisons.

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis