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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	No software was used for data collection.
Data analysis	Metabolomics: All samples were prepared at Metabolon using their automated MicroLab STAR system from Hamilton Company (see Methods). Transcriptomics: The RNA-seq data was processed at GE Global Research using established bioinformatics software tools. Base quality control was checked and found to be excellent using Fast QC v0.10.1 from Babraham Bioinformatics [Ref. 130]. Sequencing reads were mapped (median 71%) to the annotated rat genome version, Rattus norvegicus Rnor 6.0.91, using STAR_2.5.3a aligner [Ref. 131] Transcript-abundance estimates were then generated using RSEM, which outputs the expected count for each transcript. Transcript-count normalization and differential expression analysis were performed on all samples using the DESeq2 tool. Gene set enrichment analysis (GSEA) was performed using GSEA (version 3.0) tool [Ref. 97] to identify functional pathways with the gene set collection Gene Ontology (GO) biological processes (C5), Reactome and KEGG curated genes sets (C2) and the hallmark gene sets (H) available at the Molecular Signatures Database (MSigDB) (see Methods). All statistical analyses were conducted via the R software (version 3.6). The Wilcoxon rank-sum test, a non-parametric statistical hypothesis test, was used to compare any two related samples, unless otherwise stated.

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 main data supporting the results in this study are available within the manuscript and its Supplementary Information. Source data for the figures are provided with this paper. The RNA-sequencing datasets generated during the study are available (details provided in the Data availability section).

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	The studies involved the use of vertebrate animals, and original preliminary tests were completed at GE Global Research (GRC) in Niskayuna, New York. GRC has its own Institutional Animal Care and Use Committee (IACUC), and all studies using animals were conducted under IACUC-approved protocols. The center has all state required certifications for animal use, and maintains appropriate assurances on file with the Office of Laboratory Animal Welfare (OLAW), and is fully accredited by AAALAC International. Submitted protocols included the following sample-size analyses: A statistical power of 0.8 was achieved using a minimum of 6 rats per condition, and was required to have sufficient power to reject the null hypothesis (on the basis of our preliminary data; plus additional rats to allow for drop-out and/or other variabilities). This analysis was based on preliminary data outlined in: Cotero, V., Fan, Y., Tsaava, T. et al. Noninvasive sub-organ ultrasound stimulation for targeted neuromodulation. Nat Commun 10, 952 (2019), https://doi.org/10.1038/s41467-019-08750-9; and Puleo and Cotero; Noninvasive Neuromodulation of Peripheral Nerve Pathways Using Ultrasound and Its Current Therapeutic Implications Cold Spring Harb Perspect Med February 2020; 10:a034215.
Data exclusions	No data were excluded.
Replication	Replication was performed across institutions. The original whole blood glucose/HOMA-IR results (from GE Research) were first reproduced by third-party Feinstein Institutes for Medical Research (FIMR). OGTT measures were also performed at both institutions in multiple animal models. Hyperinsulinemic/euglycemic clamps were first performed at Yale University, and then replicated at FIMR in a different model or species. In vitro ion-channel blocker studies were first performed at UCLA, and then replicated in vivo at the GE facility. Additional nerve-recording confirmation was performed at AMC, supporting ELISA/IHC data at the GE site.
Randomization	All animals were randomly assigned into treatment vs. sham groups as described in Methods. The exceptions involve the swine non-terminal studies, in which each animal was tested with pFUS and sham (that is, serving as their own internal control).
Blinding	The investigators stimulating the animals knew if the pFUS system was on or off during the procedures (this was necessary, to enable stimulation with the active pfUS instrument or sham).

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

ELISA kits were purchased and used as specified by the vendors.

Insulin (Cat# 90060), leptin (Cat: 90040) and GLP-1 (Cat: 81507) ELISA kits were purchased from Crystal Chem (Elk Grove Village, IL).

IRS-1 (F34735), ghrelin (LS-F39413), GLUT4 (LS-F5891), NPY (LS-F5408), POMC (LS-F8723), KATP channel (LS-F8492-1), AMPK (LS-F36060) ELISA kits were purchased from LS-Bio (Seattle, WA).

Glutamate (ab83389), Glycogen (ab65620) and BDNF ELISA kits were purchased from Abcam (Cambridge, MA).

The GABA (E4457) ELISA kit was purchased from Biovision (Milpitas, CA).

IHC and cFOS: Primary antibody c-Fos (Santa Cruz-SC52; sc-166940)

Validation

Validation procedures of antibodies at GE have been published:
Michael J. Gerdes et al. Proc. Natl. Acad. Sci. USA, 110 (29) 11982–11987 (2013); DOI: 10.1073/pnas.1300136110, and
Cotero, V. et al. Noninvasive sub-organ ultrasound stimulation for targeted neuromodulation. Nat Commun. 10, 952 (2019); https://doi.org/10.1038/s41467-019-08750-9

Animals and other organisms

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

Laboratory animals

Adult male ZDF rats (Charles River, Kingston, NY USA) were ordered for arrival prior to 8 weeks of age. Adult male Sprague-Dawley rats (Charles River, Kingston, NY USA) were ordered to arrive at 8 weeks of age. Upon arrival, the animals were placed on a high-fat diet (45% kcal as fat; Research Diet, D12451; New Brunswick, NJ) and maintained consistently for 8 weeks. Following 8 weeks of a high-fat diet, rats were treated with streptozotocin (STZ; 30mg/kg in 0.1M citric acid buffer, pH=4.5 i.p.); 6–8 week old C57BL/6J mice (Jackson Laboratories, Bar Harbor, ME) were fed regular chow for 10 d in a reverse light cycle room, and then switched to a Western Diet (WD, D12492, 60% kcal from fat + sugar supplemented water 55% fructose, 45% sucrose), or its corresponding isocaloric low-fat control diet (10% kcal from fat) for 16 weeks. Mice in the high-fat WD group received sugar-supplemented water (55% fructose, 45% sucrose).; Adult male Yucatan miniature pigs (Exemplar Genetics, Sioux Center, IA) weighing 50–55 kg were examined by an attending veterinarian on arrival to the facility.

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not involve samples collected from the field.

Ethics oversight

GE: All procedures performed were done in accordance with the National Institutes of Health (NIH) Guidelines, under protocols approved by the Institutional Animal Care and Use Committee (IACUC) of GE Global Research.

FIMR: All procedures were performed in accordance with the National Institutes of Health (NIH) Guidelines, under protocols approved by the Institutional Animal Care and Use Committee (IACUC) of the Feinstein Institutes for Medical Research, Northwell Health.

Yale: All the animal procedures were approved by the Yale University Institutional Animal Care and Use Committee.; AMC: All animal use in the study complied with the National Institutes of Health and Albany Medical College (AMC) Institutional Animal Care and Use Committee (IACUC) guidelines.

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