### Reporting Summary

Nature Research 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 Research 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.

| Item                                                                 | 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

Cyclic voltammetry (CV) a potentiostat (SP-200, BioLogic) with EC-Lab software (v. 1.33, BioLogic). Galvanostatic charge/discharge were measured using a source meter (Keithley 2636A, Tektronix, Inc.) where control and data acquisition were performed using custom LabVIEW program (v. 2013 13.0.1, National Instruments). Voltage transients were measured using a potentiostat (SP-200, BioLogic) with EC-Lab Express software (v. 5.56, BioLogic).

For in vitro experiments, square current waveforms were delivered using a source meter (Keithley 2636A, Tektronix, Inc.) where control and data acquisition were performed using custom LabVIEW program (v. 2013 13.0.1, National Instruments). Time base for control and data acquisition set in LabView program was approximately 50 ms.

Left ventricular pressures (LVP) and perfusion pressure were monitored using a BP-100 probe (iWorx). ECG and EMG recordings were acquired using a C-ISO-256 preamplifier (iWorx). Perfusion, LVP, ECG and EMG. G signals were amplified using an IA-400D amplifier (iWorx) and interfaced with a PC using a DigiData 1550 digitizer using Clampex software (v. 10.4.0.36, Molecular Devices). Current pulses were delivered using a potentiostat (SP-200, BioLogic) controlled using EC-Lab Express software (v. 5.56, BioLogic). To synchronize time base between instruments during stimulation experiments, TTL signal was sent from DigiData 1550 digitizer to SP-200 Analog 1 input. Time base of data acquisition was 100 μs for DigiData 1550 and 140 μs for SP-200.

Data from custom-built two-photon microscope (Bruker) equipped with a Ti:sapphire laser (Chameleon Ultra II; Coherent Technologies) tuned to 920 nm was acquired using PrairieView 5.4 (Bruker).

COMSOL Multiphysics 5.5 software was used for simulations.

#### Data analysis

Analysis of numerical data was performed using Microsoft Excel for Office 365 (v.16.0), OriginPro 2016 (v. 9.3) or Python (v. 3.7.4) scripts. Statistical analyses were performed using GraphPad Prism (v. 8.4.3). Plotting was performed using OriginPro2016 (v. 9.3), Adobe Illustrator (24.3) or Python (v. 3.7.4) scripts using matplotlib library (v. 3.1.1). Confocal microscope images and imaging data were processed and...
analyzed using Leica LAS AF Lite and ImageJ (Fiji, v. 2.0.0-rc-68). The average intensities in retina experiment were processed using custom MATLAB 2019b scripts for calculation and background subtraction. The pacing frequencies in subthreshold stimulation experiment were analyzed using Python (v. 3.7.4) script using methods described in Supplementary Information. Electron microscopy data were analyzed using ImageJ (Fiji, v. 2.0.0-rc-6). EDX data were processed using AZtec (v. 4.3, Oxford Instruments). Photomasks were designed in AutoCAD 2017.1.2.

For manuscripts using 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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Raw data used in this study are available upon reasonable request. LabVIEW control program, and MATLAB and Python scripts are available at https://github.com/uchicago-Tian-Lab/Fang_et_al_Nat_Nanotechnology_2020.

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**

Sample size was not calculated beforehand. Sample size was determined based on extensive laboratory experience and literature in the field. The number of biological and technical replicates we aimed for was at least 3 with technical replicates in each group so that the number of biological and technical replicates is necessary to convince us that the effect was real. Specific sample size has been indicated in the figure legends.

**Data exclusions**

Representative images were shown in the manuscripts; similar results from experimental repeats were not shown. No data excluded for statistical analyses.

**Replication**

All experimental findings were reliably reproduced and each experiment was reproduced with similar results. Reproducibility has been indicated in the figure legends.

**Randomization**

The same type of materials, cells and animals were used for all experiments and for all experiments, animals were randomly assigned to groups. For biological images, cells were examined at several random locations.

**Blinding**

Experimenters were blinded during imaging experiments. Biocompatibility tests and stimulation experiments were not performed blind to the conditions of the experiments as treatments were determined beforehand and animal were selected in order to acquire sufficient sample size per experimental group. All subsequent sample processing was done blinded.

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

| Number | Involved in the study |
|--------|------------------------|
| n/a    |                        |
| □      | Antibodies             |
| □      | Eukaryotic cell lines  |
| ☒      | Palaeontology and archaeology |
| □      | Animals and other organisms |
| □      | Human research participants |
| □      | Clinical data          |
| □      | Dual use research of concern |

### Methods

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

**Antibodies used**

Immunostaining:

Primary antibodies: Rabbit anti-cardiac troponin I antibody (Abcam ab47003, 1:400); chicken anti-vimentin antibody (Abcam ab24525, 1:500); mouse anti-Connexin 43 antibody (Sigma Aldrich MAB3067, 1:100).

Secondary antibodies: Alexa Fluor 488 - labeled goat anti-rabbit IgG (H+L) (1: 250, A-11008, Life Technologies); Alexa Fluor 594 - labeled goat anti-chicken IgY (H+L) (1: 250, A-32759, Life Technologies); Alexa Fluor 647 - labeled goat anti-mouse IgG (H+L) (1: 250, A-28121, Life Technologies);

Detailed product information is available on the company’s website.

**Validation**

Immunostaining antibodies:

Chicken anti-Vimentin antibody has been validated by western blots and immunofluorescence staining, and reacts with vimentin from a wide range of species, including rat, mouse, and human. Totally 52 references are available for this antibody. Detailed information is available on the company’s website.

Rabbit anti-cardiac troponin I polyclonal antibody has been validated by western blots and immunofluorescence staining, and reacts with troponin I from a wide range of species, including rat, mouse, human and pig. Totally 77 references are available for this antibody. Detailed information is available on the company’s website.

Mouse anti-connexin-43 antibody has been validated by western blots and immunofluorescence staining, and reacts with connexin-43 from a wide range of species, including rat, mouse, pig, and canine. More than 80 references are available for this antibody. Detailed information is available on the company’s website.

Eukaryotic cell lines

Policy information about cell lines

**Cell line source(s)**

Primary rat cardiac fibroblasts (RCFs) and primary cardiomyocytes were isolated from hearts that excised from P0-5 neonatal rats. A Pierce™ primary cardiomyocyte isolation kit (Thermo Fisher Scientific) was used for digesting the tissue according to manufacturer protocol.

**Authentication**

Primary cardiomyocytes were authenticated with immunofluorescence staining against cardiomyocyte markers including cardiac troponin and connexin-43. Primary rat cardiac fibroblasts were authenticated with staining against vimentin.

**Mycoplasma contamination**

All cell lines were tested negative for mycoplasma contamination with Venor™ GeM Mycoplasma Detection Kit (Sigma, #MP0025)

**Commonly misidentified lines**

(See ICLAC register)

No commonly misidentified cell lines were used.

Animals and other organisms

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

**Laboratory animals**

Transgenic mice (Slc17a6tm2(cre)LowI/Gt(Rosa)26Sortm95.1(CAG-GCaMP6f)Hze) expressing the calcium indicator GCaMP6 were used in retina experiments.

6-8 week old C57BL/6J mice (female and male) were used in in vivo biocompatibility experiments (H&E staining, and body weight).

Neonatal (P1-P3) Sprague-Dawley rats (female and male) from Charles River Laboratories were used for primary rat cardiac fibroblasts (CFs) and primary cardiomyocyte in vitro experiments.

Adult (10-16 weeks) Sprague-Dawley rats (female and male) from Charles River Laboratories were used for heart and nerve stimulations.

Mice and rats were housed in the animal facility of the University of Chicago. The animal room was maintained in an environment with the humidity of 40-60 % and the temperature of 18-23°C under a 12-h light/12-h dark cycle. The animals were allowed free access to food and water.

**Wild animals**

No wild animals were used.

**Field-collected samples**

No field-collected samples were used.

**Ethics oversight**

All animals were housed under pathogen-free conditions and all animal procedures were approved by the Institutional Animal Care and Use Committees (IACUC) of the University of Chicago.

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