nature portfolio

Corresponding author(s): Scott Soderling

Last updated by author(s): 2024/06/29

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	Zeiss Zen, Axion Biosystems AxIS 2.5, LI-COR Image Studio 5.2, TopScan software, Noldus Observer, Avisoft SASLab Pro
Data analysis	SAS JMP Pro 15/16, Graphpad Prism, IBM SPSS Statistics 28, Venny 2.1, ShinyGo 0.76, 0.77, Proteome Discoverer 2.5, PolySTest Tool, Axion Biosystems NeuroMetric Tool 2.2. SynGO, MAGMA.

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

Requests for data, resources, and reagents should be directed to and will be fulfilled by the Corresponding Author, Dr. Scott Soderling (scott.soderling@duke.edu). Key plasmids from this study have also been deposited to Addgene. The proteomic and MEA data generated in this study are provided in the Supplementary Information / Source Data file. The proteomic data have also been deposited in the MassIVE database under accession code MSV000095141.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	n/a
Reporting on race, ethnicity, or other socially relevant groupings	n/a
Population characteristics	n/a
Recruitment	n/a
Ethics oversight	n/a

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

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes were determined based on previous experiences (Uezu et al, Science, 2016; Courtland et al, eLife, 2021; Erata et al, J Neurosci, 2021; Wang et al, Hum Mol Genet, 2011; Pappas et al, JCI Insight, 2017). No statistical methods were used to predetermine sample sizes.
Data exclusions	No data in study groups were excluded from the analyses.
Replication	All attempts at replication (at least 3 replicates) were successful.
Randomization	Allocation was random when possible. For the MEA experiments, different groups were allocated on an alternating pattern across the plate to minimize the potential bias of plating conditions.
Blinding	Behavioral data were collected blinded to the experimental conditions. For other experiments, the investigators were not blinded to group allocation.

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
☒	☐ Plants

Methods

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

Antibodies

Antibodies used	rabbit anti-HA, Cell Signaling #3724 rat anti-HA, Sigma #11867423001 mouse anti-PSD95, Abcam #ab2723

rabbit anti-GAPDH, Abcam #ab9485
rabbit anti-GAPDH, Cell Signaling #2118
mouse anti-V5-epitope, ThermoFisher #R960-25
guinea pig anti-Homer1, Synaptic Systems #160004
mouse anti-Myc-epitope, Santa Cruz #sc-40
rabbit anti-V5-epitope, Cell Signaling #13202S
rabbit anti-GFP, Cell Signaling #2956S
goat anti-SYNGAP1, Sigma #SAB2501893
rabbit anti-SYNGAP1, ThermoFisher #PA5-58362
rabbit anti-ANKS1B, ThermoFisher #PA5-98554
rabbit anti-SHANK2, Cell signaling #12218S
mouse anti-AnkyrinG, ThermoFisher #33-8800
mouse anti-NaV1.2, Antibodiesinc #75-024
mouse anti-ANKS1B, Santa Cruz #sc-376610
Alexa Fluor and IRDye conjugated secondary antibodies.

Validation

Antibodies were chosen based on reviewing validation data provided by the manufacturers and literature citing these antibodies. Validation information about these commercial antibodies can be found on the manufacturers' websites:
rabbit anti-HA, Cell Signaling #3724
https://www.cellsignal.com/products/primary-antibodies/ha-tag-c29f4-rabbit-mab/3724
rat anti-HA, Sigma #11867423001
https://www.sigmaaldrich.com/US/en/product/roche/roahaha
mouse anti-PSD95, Abcam #ab2723
https://www.abcam.com/psd95-antibody-6g6-1c9-synaptic-marker-ab2723.html
rabbit anti-GAPDH, Abcam #ab9485
https://www.abcam.com/gapdh-antibody-loading-control-ab9485.html
rabbit anti-GAPDH, Cell Signaling #2118
https://www.cellsignal.com/products/primary-antibodies/gapdh-14c10-rabbit-mab/2118
mouse anti-V5-epitope, ThermoFisher #R960-25
https://www.thermofisher.com/antibody/product/V5-Tag-Antibody-Monoclonal/R960-25
guinea pig anti-Homer1, Synaptic Systems #160004
https://sysy.com/product-factsheet/SySy_160004
mouse anti-Myc-epitope, Santa Cruz #sc-40
https://datasheets.scbt.com/sc-40.pdf
rabbit anti-V5-epitope, Cell Signaling #13202S
https://www.cellsignal.com/products/primary-antibodies/v5-tag-d3h8q-rabbit-mab/13202
rabbit anti-GFP, Cell Signaling #2956S
https://www.cellsignal.com/products/primary-antibodies/gfp-d5-1-rabbit-mab/2956
goat anti-SYNGAP1, Sigma #SAB2501893
https://www.sigmaaldrich.com/US/en/product/sigma/sab2501893
rabbit anti-SYNGAP1, ThermoFisher #PA5-58362
https://www.thermofisher.com/antibody/product/SynGAP-Antibody-Polyclonal/PA5-58362
rabbit anti-ANKS1B, ThermoFisher #PA5-98554
https://www.thermofisher.com/antibody/product/ANKS1B-Antibody-Polyclonal/PA5-98554
rabbit anti-SHANK2, Cell signaling #12218S
https://www.cellsignal.com/products/primary-antibodies/shank2-antibody/12218
mouse anti-AnkyrinG, ThermoFisher #33-8800
https://www.thermofisher.com/antibody/product/Ankyrin-G-Antibody-clone-4G3F8-Monoclonal/33-8800
mouse anti-NaV1.2, Antibodiesinc #75-024
https://www.antibodiesinc.com/products/anti-nav1-2-na-channel-antibody-k69-3-75-024
mouse anti-ANKS1B, Santa Cruz #sc-376610
https://www.scbt.com/p/aida-1-antibody-c-10

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	HEK293T cell line was obtained from American Type Culture Collection (ATCC)
Authentication	The cell line was validated by STR testing.
Mycoplasma contamination	The cell line was tested for mycoplasma contamination and was negative.
Commonly misidentified lines (See ICLAC register)	n/a

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	P0-P28 male and female H11-Cas9 mice (Jackson Laboratory), P0-2 and adult male and female Scn2a(+/R102Q) mice (generated by the Duke Transgenic and Knockout Mouse Shared Resource), adult male and female Syngap1-Het mice (a gift from Dr. Gavin Rumbaugh), adult C57BL/6J females (Jackson Laboratory), adult C3H/HeJ males (Jackson Laboratory). Mice were group-housed in the Duke University's Division of Laboratory Animal Resources facility, with an ambient temperature of 72 +/- 2 Fahrenheit, humidity of 30-70%, and light cycle of 12 hrs on/off.
Wild animals	This study did not involve wild animals.
Reporting on sex	Animals of both sexes were used in this study, except for the social interaction tests where data were collected only from male mice.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	The Duke University Institutional Animal Care and Use Committee provided ethical approval and guidance.

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

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a