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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	The µManager plugin (Version 1.4) in ImageJ was used for IOS and GWI image acquisition. For in vivo GCaMP imaging, we acquired images using ScanImage 5.2 software, running on MATLAB (2013b). To replicate noise associated with the resonant scanner, Avisoft-Recorder (USGH 4.2.27) and Avisoft-SASLab Pro (5.2.12) software was used. For in vivo electrophysiology experiments, data was acquired by a custom in vivo whole cell patch clamp system, with a National Instruments acquisition system in MATLAB (2015b), as previously described (Desai et al., 2015). Neurolucida 360 (V.2017.01.1) was used to generate three-dimensional neuron tracings. For slice electrophysiology experiments, data was acquired using Clampex (10.2) software from the PCLAMP10 Software Suite (Molecular Devices). Ethovision XT (11.5) was used for the novel texture discrimination task. BControl software (C. Brody) running on MATLAB (2013a) was used to control the Go/NoGo apparatus.
Data analysis	Custom scripts written in MATLAB (2015b), as well as the IO and VSD Signal Processor (Version 1.0.8) plugin in ImagJ were used to analyze IOS and GWI imaging data, while cellular GCaMP imaging data was analyzed using FluoroSNNAP15.04.08 running on MATLAB (2015b). Motion artifacts were corrected with the moco plugin (03-18-2016) in ImageJ, while ImageJ (Version 1.50) was used to analyze Mcherry fluorescence. Visualization and analysis of three-dimensional neuron tracings was performed with NeuroExplorer (Version 4). For electrophysiology experiments, data was analyzed using Clampfit (10.2, Molecular Devices) software. Ethovision XT (11.5) was used for data analysis of the novel texture discrimination task. Basic whisking was scored manually, offline using Solomon Coder (17.03.22). Statistical analysis was performed in MATLAB (2015b), GraphPad Prism 7, Excel (16.14.1) and SPSS (Version 20).

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/reviewers upon request. 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

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	No statistical methods were used for determining sample sizes. However, our sample sizes are similar to those previously reported in the field (He et al., 2017,).
Data exclusions	Exclusion criteria for experimental data points were pre-determined as follows. Animal death during anesthetized experiments or deterioration of cranial window clarity during imaging experiments (limited to < 5% of cases), as reliable data acquisition could not be verified under these conditions. For neuronal morphology studies, only neurons with the following criteria were selected for tracing: 1) neuron was selected starting toward the middle of the stack (~150 µm ± 30 µm) to ensure the accurate reconstruction of an entire dendritic arbor; 2) neuron was distinct from other neurons to allow for identification of branches; 3) neuron was not truncated in some obvious way. For in vitro whole-cell patch clamp experiments cells with access resistance >30 MΩ or were unstable (>20 % change) were discarded from further analysis. For texture discrimination testing, mice that did not explore objects during the learning phase, explored only one of the two objects during the testing phase, or had a total investigation time of less than 20 s during the learning phase, were excluded from the study for lack of adequate exploratory activity.
Replication	We attempted to replicate data whenever possible by using multiple cohorts of animals (typically two), for imaging and behavior experiments. Results were reliably reproduced in these cases. We are encouraged by the fact that the cellular sensory properties in response to passive whisker stimulations in our imaging studies were repeatable in multiple mouse lines tested, including the Thy1-GCaMP6s4.3 x Syngap1, EMX1-Cre x Syngap1 cKO and Gad2-NLS-mCherry x Syngap1 lines. Furthermore, the resulting reduced neural responsiveness to passive whisker stimuli in awake Botox-treated (non-whisking) Thy1-GCaMP6s4.3 x Syngap1 animals was similar to those from the EMX1-Cre x Syngap1 cKO line under anesthesia, suggesting a repeatable phenotype across experimental conditions (ie. brain state). Our results from the Go/NoGo task were repeatable in our lab as this data was pooled from two separate cohorts that were conducted by two independent experimenters.
Randomization	Generation of multiple transgenic mouse lines was labor, time and resource intensive. Additionally, most experiments required 1-3 months to complete, even with small sample sizes. This prevented us from picking WT and Het animals randomly from litters. Therefore, to obtain comparable sample sizes between genotypes, animal cohorts were generated by allocating relatively equal number of age-matched Syngap1 WT and Het littermates from separate litters, usually more than two. Then, animals were assigned a number to hide identity of genotype and/or group assignment. For imaging and behavior tasks, animals were recorded once per day in a randomized order while blinded to genotype. For imaging experiments, stimulations were presented in a pseudo-random sequence for each imaging depth.
Blinding	For all studies, experimenters were blinded to genotype at the time of data acquisition and analysis.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Animals and other organisms

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

Laboratory animals	The conventional and conditional Syngap1+/- mouse lines have been previously described (Kim et al., 2003, Clement at al., 2012) and maintained on a BL6/B129sv/ev hybrid genetic background. Thy1-GCaMP6s4.3 (#024275), Emx1-Cre (#05628), Gad2-NLS-mCherry (#023140), and the TdTomato Ai9 (#007905) reporter mouse lines were purchased from Jackson Laboratories and maintained on a pure C57BL/6J background. Rbp4-Cre (037128-UCD) and Cux2-CreERT2 (032779-MU) mouse lines were purchased from MMRC and maintained on a pure C57BL/6J background. Both males and females were used in all experiments indiscriminately, except for the Go/NoGo task, where only males were used. Data collection occurred from mice >8 weeks of age.
Wild animals	The study did not involve any wild animals.
Field-collected samples	The study did no involve any field-collected animals.

Human research participants

Policy information about studies involving human research participants

Population characteristics	The SYNGAP1 patient population was self-identified in the Registry. There were no entrance exclusions and anyone could join, upload medical records, medical data and answer questionnaires. Because of this, it was crucial to focus on patients in the sensory survey that included conclusive genetic information (i.e. a genetic report from a medical geneticist). These patients can be found in Supplementary Table 2.
Recruitment	Participants (parents or guardians) volunteered and provided informed consent prior to depositing medical data into the registry. There were no entrance exclusions and anyone could join, upload medical records, medical data, and answer questionnaires. Because of this, it was crucial to focus on patients in the registry that included conclusive genetic information (i.e. a genetic report from a medical geneticist). These patients can be found in Supplementary Table 2.