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Corresponding author(s): Viviana Gradinaru

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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 Authors & Referees 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	ImageJ/FIJI 1.51, Image Lab (Bio-Rad) 6.0.1, Python 3.7.2, Zen (Zeiss) 14.0.0.0, Solis (Andor) 4.31.30022
Data analysis	Python 3.7.2 (pandas, seaborn), GraphPad Prism 6, ImageJ/FIJI 1.51, Image Lab (Bio-Rad) 6.0.1

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. 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

No datasets were generated or analysed during the current study

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 estimated number of animals needed to attain >90% power for each experiment was based on an expected effect size of 0.7 calculated from preliminary experiments comparing wild type to α-synuclein overexpressing mice. Power analysis was performed using a SAS based model for multifactorial ANOVA designs.
Data exclusions	No data points were excluded from statistical analysis. Outliers that were 1.5x outside of the 25th/75th interquartile range were not plotted on graphs for presentation purposes.
Replication	Experiments involving mice were performed using 2+ cohorts initiated at different times. Attempts at replication were successful.
Randomization	For given age-matched animal cohorts, mice were evenly divided between the experimental conditions.
Blinding	Behavioral analysis was performed blinded and condition revealed after analysis was completed.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used

1. Mouse IgG2a monoclonal anti-α-synuclein phospho (Ser129, Clone81A) (BioLegend MMS-5091, lot #B230550, Duodenum IHC 1:300, Brain IHC 1:500)
2. Rabbit polyclonal anti-α-synuclein phosphor (Ser129) (Abcam ab59264, lot #GR52476-60, Western 1:500)
3. Rabbit monoclonal anti-Alpha-synuclein filament antibody [MJFR-14-6-4-2] - Conformation-Specific (Abcam ab209538, lot#GR293949-11, Dot blot 2ng/mL)
4. Rabbit polyclonal anti-Protein gene product 9.5 (PGP9.5) (Millipore AB1761-I, lot #2581358, Duodenum IHC 1:300, Nodose IHC 1:100)
5. Chicken polyclonal anti-Protein gene product 9.5 (PGP9.5) (ThermoFisher Scientific PA1-10011, lot # TI2631136, Duodenum IHC 1:300)
6. Chicken polyclonal anti-Glial fibrillary acidic protein (GFAP) (Millipore AB5541, lot # 2728385, Duodenum IHC 1:300)
7. Goat polyclonal anti-Choline acetyltransferase (ChAT) (Millipore AB144P, lot #2620146, Brain IHC 1:500)
8. Rabbit polyclonal anti-Tyrosine hydroxylase (TH) (Millipore AB152, lot #2665965, Brain IHC 1:500)
9. Chicken polyclonal anti-Green fluorescent protein (GFP) (Aves Labs GFP-1010, lot #GFP697986, Brain IHC 1:1000)
10. Rabbit polyclonal anti-Red fluorescent protein (RFP) (Rockland 600-401-379, lot #35868, Brain IHC 1:1000)
11. Rabbit polyclonal anti-GBA1 (Abcam ab175869, lot #GR221342-17, Western 1:1000)
12. Rabbit polyclonal anti-Interleukin 6 (IL6) (Abcam ab7737, lot #GR3185165-1, Western 1:500)
13. Rabbit polyclonal anti-Iba1 (Wako 016-20001, lot # LKH4161, Western 1:1000)
14. Rabbit polyclonal anti-β-Tubulin (Abcam ab6046, Western 1:1000)
15. Mouse IgG2b anti-β-actin (Cell Signaling 3700, Western 1:1000)
16. AlexaFluor 488 Goat anti-Mouse IgG2a (ThermoFisher Scientific A-21131, IHC 1:300-1000)
17. AlexaFluor 488 Donkey anti-Mouse IgG (ThermoFisher Scientific A-21202, IHC 1:300-1000)
18. AlexaFluor 488 Donkey anti-Chicken IgY (Jackson ImmunoResearch 703-545-155, IHC 1:300-1000)
19. AlexaFluor 555 Donkey anti-Rabbit IgG (ThermoFisher Scientific A-31572, IHC 1:300-1000)
20. AlexaFluor 555 Donkey anti-Goat IgG (ThermoFisher Scientific A-21432, IHC 1:300-1000)
21. AlexaFluor 633 Goat anti-Rabbit IgG (ThermoFisher Scientific A-21071, IHC 1:300-1000)
22. AlexaFluor 633 Goat anti-Chicken IgY (ThermoFisher Scientific A-21103, IHC 1:300-1000)
23. Horseradish peroxidase (HRP)-linked Goat anti-Rabbit IgG (CellSignaling 7074, Western, dot blot 1:2000)
24. Horseradish peroxidase (HRP)-linked Goat anti-Mouse IgG (CellSignaling 7076, Western 1:2000)
25. Horseradish peroxidase (HRP)-linked Goat anti-Mouse IgG2a (Abcam ab97245, Western 1:2000)

Validation

Antibodies were only used if validated by the manufacturer via their website. Most antibodies used are standard in the field and

are cited in the manuscript where relevant:
1. Use of antibody for immunohistochemistry (IHC) was validated in mouse brain tissue in Adamowicz DH, et al. 2017. J. Neurosci. 37(7):1675-1684.
2. Use of antibody for Western blot was validated by Abcam using brain extracts from transgenic mice overexpressing human alpha-synuclein at a dilution of 1:1000.
3. Use of antibody for dot blot was validated by Abcam via Professor Paul Henning Jensen against recombinant alpha-synuclein filaments with 2.2 ng/mL of antibody.
4. Use of antibody for IHC was validated by Millipore using cultured rat cortical cells at a dilution of 1:100.
5. Use of antibody for IHC was validated by ThermoFisher in cortical neuron-glia co-cultures at a dilution of 1:2000.
6. Use of antibody for IHC was validated by Millipore using cultured rat neonatal forebrain cells at a dilution of 1:500 and is evaluated by Western blot on mouse brain lysates.
7. Use of antibody for IHC was validated by Millipore via D. Anandh, K Shobha and Dr. Bindu M Kutty in rat neocortex and is evaluated by Western blot on mouse brain lysates.
8. Use of antibody for IHC was validated by Millipore in mouse primary neural cultures at a dilution of 1:1000 and is evaluated by Western blot on PC12 cell lysates.
9. Use of antibody was validated by Western blot analysis (1:5000 dilution) and IHC (1:500 dilution) using transgenic mice expressing the GFP gene product.
10. Use of antibody for IHC was validated by Rockland by staining retina tissue from DsRed transgenic mouse at a dilution of 1:10,000 and by Western Blot for recombinant RFP protein.
11. Use of antibody for Western blot was validated by Abcam using mouse lung lysate at a dilution of 1:1000.
12. Use of antibody for Western blot was validated by Abcam at a dilution of 1:20 and in Cao W, et al. 2018. Front Immunol. 9:647.
13. Use of antibody for Western blot was validated by Wako via Sanagi,T., Ichinohe, N., and Kohsaka, S using purified Iba1 protein and rat microglia at a dilution of 1:1000.
14. Use of antibody as a loading control for Western blot was validated by Abcam using HeLa cell lysate, A431 cell lysate, MCF7 cell lysate, and 293 cell lysate at a dilution of 1:500.
15. Use of antibody as a loading control for Western blot was validated by Cell Signaling using various cell types at a dilution of 1:1000.
16. Use of antibody for secondary detection in IHC was validated by ThermoFisher in HeLa cells at a concentration of 1 µg/mL.
17. Use of antibody for secondary detection in IHC was validated by ThermoFisher in MCF-7 cells at a concentration of 0.2 µg/mL.
18. Use of antibody for secondary detection in IHC was validated in Durand de-Cuttoli R, et al. 2018. Elife. pii: e37487 at a dilution of 1:1000.
19. Use of antibody for secondary detection in IHC was validated by ThermoFisher in HeLa cells at a concentration of 4 µg/mL.
20. Use of antibody for secondary detection in IHC was validated in Sauvegarde C, et al. 2016. PLoS One. 11(10):e0165898 at a dilution of 1:500.
21. Use of antibody for secondary detection in IHC was validated by ThermoFisher in HepG2 cells at a concentration of 4 µg/mL.
22. Use of antibody for secondary detection in IHC was validated in Chen Z, et al. 2013. J Neurosci. 33(19):8336-51 at a dilution of 1:2000.
23. Use of antibody for secondary detection in Western blots was validated in Shaw JH, et al. 2018. Front Cell Infect Microbiol. 8:415 at a dilution of 1:1000.
24. Use of antibody for secondary detection in Western blots was validated in Jeong JH, et al. 2018. PLoS Biol. 16(4):e2004399 at a dilution of 1:3000.
25. Use of antibody for secondary detection in Western blots was validated by Abcam at dilutions of 1:2000-1:20000.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293T (ATCC, CRL 3216; for virus production)
Authentication	Cell line was authenticated by production of AAV9-CAG-mNeonGreen virus, which was validated in cell culture
Mycoplasma contamination	The cell line was tested negative for mycoplasma
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	C57BL/6N mice (males, 8-10 weeks old or 16 month old); Thy1-α-synuclein overexpressing mice (males, 6 month or 12 month old; generated by crossing female BDF1/Thy1-α-synuclein mice heterozygous for transgene to wild type male BDF1)
Wild animals	Study did not use wild animals
Field-collected samples	Study did not use field-collected samples
Ethics oversight	Care and experimental manipulation of animals were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Caltech Institutional Animal Care and Use Committee.

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