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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.

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

1. AFM imaging: XE data acquisition program (XEP 1.8.0) provided by XE-100 AFM (Park Systems).
2. TEM imaging: Phillips EM 410 TEM with a Soft Imaging System Megaview III digital camera, equipped in a Phillips CM 120 TEM.
3. 1H-15N HSQC spectra were processed by NMRPipe.
4. Molecular dynamics simulation was performed with Gromacs 5.1 software and the adapted α-syn structure (PDB 1D: 2N0A) was processed with CHARMM forcefield. GQDs stucture for simulation was designed with CGenFF by the protocols of (https://cgenff.paramchem.org).
5. Stereological assessments of TH- and Nissl-positive neurons were counted using an Optical Fractionator probe of Streo Investigator software (MBF Bioscience).

Data analysis	1. All relevant images for dot-blot assay, BN-PAGE & SDS-PAGE, mitochondrial morphology assessments, in vitro and in vivo immunohistochemcial analyses were quantified using ImageJ software (http://rsb.info.nih.gov/ij/, NIH). 2. 1H-15N HSQC spectra were analysed by Sparky. 3. The fractional secondary structure contents of α-syn were calculated by the algorithm of CONTIN/LL on the DichroWeb online server (http://dichroweb.cryst.bbk.ac.uk), where the reference set #7 optimised for 190 - 240 nm was used. 4. For the statistics, Student's t tests or ANOVA tests followed by Bonferroni post hoc analysis were performed using Prism6 software (GraphPad). - Further detailed information including the references for the utilized softwares are described in the Methods section.

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

- There is no data relevant to accession codes or unique identifiers non-publicly available. All generated data are included in the manuscript and available by either B.H.H or H.S.K 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 to pre-determine the sample sizes but they were determined based on the previous literatures(1-4) 1. Mao et al., Science. 2016; 335(6307) 2.Brahmachari et al., J Clin Invest 2016; 126(8): 2970-88 3. Luk et al., Science. 2012; 338(6109): 949-53 4. Peelaerts et al., Nature. 2015; 522: 340-4
Data exclusions	- No data were excluded from the analyses.
Replication	- All attempts were successful. All results relevant to the replicated trials were obtained independently by two different laboratories and researchers for reliability.
Randomization	- For behavioural tests and cell death assays, the investigators were allocated to the randomized groups.
Blinding	- The investigators in all experiments were blinded to the groups and samples during data collection except for Western blot and dot-blot.

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

Antibodies

Antibodies used

- All antibodies used in the study are described in the Methods section in detail, which include the catalogue number, dilution factor, providers and etc. All antibodies used in the study were already verified in the previous literatures (1-4).
1. Mao et al., Science. 2016; 335(6307)
2. Brahmachari et al., J Clin Invest 2016; 126(8): 2970-88
3. Luk et al., Science. 2012; 338(6109): 949-53
4. Kim et al., PNAS. 2010; 107(33) 14851-6
Antibodies' details:
MAP2 (Millipore, Cat#: MAB3418, clone AP20, Lot#: 2905344, 1:1,000)
p-alpha-Syn (abcam, Cat#: ab59264, Lot#: GR52476-37, 1:1,000)
alpha-Syn filament (abcam, Cat#: ab209538, 1:1,000)
beta-actin peroxidase(Sigma, Cat#: A3854, clone AC15, 1:50,000)
Tyrosine Hydroxylase (Novus, Cat#: NB300-109, 1:1,000)
SNAP25 (Synaptic systems, Cat#: 111-002, 1:2,000)
VAMP2 (abcam, Cat#: ab3347, 1:1,000)
8-OHG (abcam, Cat#: ab62623, clone 15A3, 1:1,000)
CD31 (abcam, Cat#: ab28364, 1:500)
GFAP (Dako, Cat#: Z0334, 1:2,000)
Iba-1 (Wako, Cat#: 019-19741, 1:1,000)

Validation

- The validation was performed by the commercial supplier.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

- HEK293 cells were used in the study, which were provided by American Type Culture Collection (ATCC).

Authentication

- The authentication was performed by the commercial supplier.

Mycoplasma contamination

- Cells were routinely tested for mycoplasma contamination and found to be negative.

Commonly misidentified lines
(See ICLAC register)

- We did not use any commonly misidentified cell lines.

Animals and other organisms

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

Laboratory animals

- All in vivo experimental procedures were followed according to the guidelines of Laboratory Animal Manual of the National Institute of Health Guide to the Care and Use of Animals, which were approved by the Johns Hopkins Medical Institute Animal Care and Use Committee.
(1) Mouse strain for α-syn PFFs injection. 8-10 weeks male C57BL/6 mice were obtained from the Jackson Laboratories. The mice do not develop any autoimmune or inflammatory phenotype. GQDs was IP injected for 6 months.
(2) hA53T α-syn transgenic mice. hA53T α-syn transgenic mice (mixed male and female) were obtained from Jackson Laboratories (B6; Prnp-SNCA*A53T; Cat#: 006823). GQDs was IP injected to 6 months old hA53T α-syn transgenic mice until 10 months of age.

Wild animals

Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.

Field-collected samples

For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.