nature research

Corresponding author(s): Simon N. Waddington

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	The evaluation of the immunoreactivity of stained sections was performed using the Image-Pro Premier analysis system (Media Cybernetics, Rockville MD, USA). Neuron counting and cortical thickness measurements were estimated with Stereo Investigator software (MBF Bioscience, Williston VE, USA).
Data analysis	The statistical analysis was performed with GraphPad Prism Software (v. 6.0e). The evaluation of the immunoreactivity of stained sections was performed using the Image-Pro Premier analysis system (Media Cybernetics, Rockville MD, USA). Neuron counting and cortical thickness measurements were estimated with Stereo Investigator software (MBF Bioscience, Williston VE, USA).

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

All data generated or analysed during this study are included in this published article (and its supplementary information files). Raw data are available online at 10.5281/zenodo.1246085. These data are also available from the corresponding author on 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	The group sizes were determined by a power calculation (power of 0.8), using PS Power & Sample size software (Dupont WD, Plummer WD, Jr. (1990). Power and sample size calculations. A review and computer program. Control Clin Trials 11(2): 116-128.). The calculation was based upon differences between groups obtained in our previous study (Rahim AA et al (2011). Intravenous administration of AAV2/9 to the fetal and neonatal mouse leads to differential targeting of CNS cell types and extensive transduction of the nervous system. FASEB J 25(10): 3505-3518.). We aimed to include two additional mice in each group in case of unexpected loss from the study (which did not occur)
Data exclusions	No data were excluded from the analyses.
Replication	All data using AAV9-GUSB-GBA vector are presented in this manuscript. We have repeated intracranial and intravenous neonatal injections using an alternative vector configuration and observe similar therapeutic efficacy
Randomization	For fetal injections, randomization was inevitable since the genotype of the injected fetuses could not be determined until after birth. Neonatal pups were randomly allocated to separate treated and untreated groups, ensuring random distribution across litters
Blinding	The operator was blinded to the genotype of the animals throughout testing and analysis of behavioral scoring. The quantification of immunohistochemical staining and stereological count of neurons were conducted by a user blinded to the experimental cohorts.

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	Rabbit anti-GFP, AB290, Abcam; Mouse anti-GBA1 N-terminus, clone OTI1D12, TA803361, Origene; Anti-GBA1 C-terminus, G4171, Sigma-Aldrich.; Rat anti-mouse CD68, MCA1957, AbD Serotech.; Mouse anti-GFAP, MAB3402, Millipore.; Rabbit anti-LAMP1, AB24170, Abcam.; Biotinylated anti-mouse IgG, BA-9200, Vector Lb Inc.; Biotinylated anti-rabbit IgG, BA-1000, Vector Lb Inc.; Biotinylated anti-rat IgG, BA-9400, Vector Lb Inc.; Lot numbers were not recorded

Validation	Rabbit anti-GFP, AB290, Abcam: suitable for IHC-FrFl analysis of mouse brain tissue sections (from abcam.com). Anti-GBA1 raised against amino acids 40-315 of human GBA; Origene: suitable for WB and IHC (from origene.com) Anti-GBA1 C-terminus, G4171, Sigma-Aldrich: mouse reactivity (from abcam.com), suitable for IHC (see data in the manuscript). Rat anti-mouse CD68, MCA1957, AbD Serotech: suitable for immunohistology of mouse tissue sections (from bio-rad-antibodies.com). Mouse anti-GFAP, MAB3402, Millipore: suitable for IHC of mouse tissue (from merckmillipore.com). Rabbit anti-LAMP1, AB24170, Abcam: suitable for IHC of mouse tissue (from abcam.com). Biotinylated secondary antibodies, Vector Lb Inc: suitable for tissue staining (from vectorlabs.com).

Animals and other organisms

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

Laboratory animals	Mice heterozygous for mutation in the GBA1 gene and carrying the Cre recombinase gene on a C57BL/6 background were outbred onto wild type CD1 mice (Charles River, Harlow, UK) for five generations. Fig 2F-M fetal IV treated KO: 3 females 2 males. Sex not recorded for Fig 2A-E IV treated KO Fig 4A-M neonatal IV treated KO: 4 males, 1 female. WT: 2 males, 1 female. IC treated KO: 1 male, 2 females. Sex not recorded for Fig 4N-P 1 male cynomolgus macaque, in utero injection at D58, Delivery at D147, Euthanasia at day 0. 1 female cynomolgus macaque in utero injection at D59, Caesarean delivery at D147, Euthanasia on day 6
Wild animals	No wild animals were used in this study
Field-collected samples	No field-collected samples were used in this study