

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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☒	☐ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give <i>P</i> values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	Microsoft Excel
Data analysis	GraphPad Prism 7, Microsoft Excel, MestReNova

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](#)

All data in this study are available and reported in the main manuscript and supporting information. The data supporting the findings of this study are available from the corresponding authors upon reasonable request.

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](https://www.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 size was determined based on power analysis and historical data using identical experimental setup that has been published previously (Biscans, A. et al. PMID: 30544191, Alterman, J. et al. PMID: 31375812, Ferguson, C. et al. PMID: 38375983, Biscans, A. et al. PMID: 33348054).

Data exclusions No exclusion

Replication All experiments were performed in biological replicates with at least two sequences and reproducibility has been confirmed.

Randomization Randomization is not relevant because all experiments used in bred genetically defined mice obtained from Charles River (The Jackson Laboratory, Bar Harbor, ME).

Blinding Not blinded in keeping with general established standards for rodent pre-clinical experiments .

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

Methods

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

n/a Involved in the study

☒ ☐ ChIP-seq

☒ ☐ Flow cytometry

☒ ☐ MRI-based neuroimaging

Antibodies

Antibodies used Anti-Vinculin (Sigma, V9131). Anti-Htt (Ab1, aa1-17, DiFiglia et al. Neuron, 1995) was produced in DiFiglia laboratory.

Validation

Validation statements for Anti-Vinculin can be found in following links to the manufacturer's website.
<https://www.sigmaaldrich.com/US/en/product/sigma/v9131#product-documentation>
 The anti-HTT antibody characterization is described fully in previous report (DiFiglia et al. PMID: 7748555) including a blocking control experiment with both competing and unrelated peptides.

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

HeLa (ATCC)

Authentication

Authenticated by manufacturer through STR analysis. The quality control specification data can be found in manufacturer's website (<https://www.atcc.org/products/ccl-2>).

Mycoplasma contamination

Negative for contamination

Commonly misidentified lines
 (See [ICLAC](#) register)

No commonly misidentified cell lines were used in the study.

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

In the study for the siRNA systemic administration, 6-8-weeks old WT-FVB female mice were obtained from Charles River (The Jackson Laboratory, Bar Harbor, ME). In the study for the siRNA ICV administration, WT FVB/NJ mice were obtained from Charles River (The Jackson Laboratory, Bar Harbor, ME). All animals were housed in the IACUC accredited animal facility at UMass Chan Medical School Institution Animal Care and housed with a maximum of 5 per cage in the pathogen-free facility under standard conditions with access to food, water and enrichment ad libitum. Dark/light ambient temperature and humidity were centrally regulated and animals were closely monitored by resident veterinarians for wellbeing.

Wild animals

The study did not involve wild animals.

Reporting on sex

All mice used in this study was female mice.

Field-collected samples

No field collected samples were used in this study.

Ethics oversight

UMass Chan IACUC

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