

## 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 ( $n$ ) 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 bcl2fastq embedded by Illumina

Data analysis  
cellranger-arc (<https://www.10xgenomics.com/support/software/cell-ranger-arc/latest>), v2.0.0  
Seurat (<https://satijalab.org/seurat/>), v4.0.5  
scVI (10.1038/s41587-021-01206-w), v1.0.3  
scANVI (doi.org/10.15252/msb.20209620), v1.0.3  
edgeR (<https://bioconductor.org/packages/release/bioc/html/edgeR.html>), v3.36.0  
fimo (<https://meme-suite.org/meme/doc/fimo.html>), v5.4.1  
monocle (<http://cole-trapnell-lab.github.io/monocle-release/docs/>), v2.22.0  
fastTopics (<https://stephenslab.github.io/fastTopics/>), v0.6-142  
GSEA (<https://www.gsea-msigdb.org/gsea/index.jsp>), v4.1.0  
CellChat (<https://github.com/jinworks/CellChat>), v1.6.1  
NeuronChat (<https://github.com/Wei-BioMath/NeuronChat>), v1.0.0

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](#)

<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE268609>

## 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                                        | This study uses de-identified postmortem frozen hippocampi. We reported sex, age and all criteria related to brain pathology. |
| Reporting on race, ethnicity, or other socially relevant groupings | This study did not report these social parameters. N/A                                                                        |
| Population characteristics                                         | N/A. This study did not recruit patients/population.                                                                          |
| Recruitment                                                        | N/A. This study did not recruit patients/population.                                                                          |
| Ethics oversight                                                   | UIC IRB, University of Washington IRB                                                                                         |

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     | n=10 hippocampi of Alzheimer's disease, n= 8 each for young adults with intact memory (YA) and aged adults with no cognitive impairments (HA), n= 6 each for patients of preclinical with intermediate pathology (PCI) and individuals with extraordinary memory capacity (SuperAgers or SA) . A total of 355,997 nuclei were sequenced. The maximum sample size available from brain banks was used. |
| Data exclusions | For sequencing, cells with >10% mitochondrial expression; cells with low numbers of genes expressed (<1000 genes) or low total UMI RNA counts (<2000 UMI counts); and cells with low peak numbers (<200 peaks) or total ATAC counts (<500 counts) were removed                                                                                                                                        |
| Replication     | Sequencing QC, validation of observations against previous datasets.                                                                                                                                                                                                                                                                                                                                  |
| Randomization   | De-identified samples were obtained from the Alzheimer's disease research centers at University of Washington and the Northwestern University Alzheimer's Disease Research Center (NU-ADRC) Brain Bank. Samples were selected by the Alzheimer's centers based on cognitive diagnosis and Alzheimer's pathology.                                                                                      |
| Blinding        | Samples that arrived from the Alzheimer's disease centers were coded. Investigators, sequencing researchers and analysts were blinded to codes.                                                                                                                                                                                                                                                       |

## 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 &amp; experimental systems

## Methods

| n/a                                 | Involved in the study                                  |
|-------------------------------------|--------------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                        |

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration *Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*

Study protocol *Note where the full trial protocol can be accessed OR if not available, explain why.*

Data collection *Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*

Outcomes *Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

## Plants

Seed stocks *Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*

Novel plant genotypes *Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*

Authentication *Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.*