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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	Summit v4.3.02 Build 2451 was used for flow cytometry.
Data analysis	Alignments and methylation calling was performed using Bismark (v14.3). Transcription factor binding motif analysis was performed with Haystack (v0.4). Differential analysis was performed using TEPIC (v2.0)/DYNAMITE (v1.0) to identify novel transcriptional regulators for differentially expressed genes. LDSC (v1.0.0) was used to estimate the proportion of genome-wide SNP-based heritability. ATAC-seq reads were trimmed with trimadap (v0.1), aligned with Bowtie2 (v2.2.5), and peaks were called using MACS (v2.1.0). All statistical analyses were performed using R (v3.3.x) and made use of packages contributed to the Bioconductor project. In addition to those R/Bioconductor packages specifically referenced in the above, we made use of several other packages and online programs in preparing results for the manuscript: bsseq (v1.14), AnnotationHub (v2.6.4), biomaRt (v2.30.0), GenomicAlignments (v1.10.0), GenomicFeatures (v1.26.2), GenomicRanges (v1.26.2), ggplot2 (v2.2.1), Hmisc (v4.0-2), Matrix (v1.2-8), rtracklayer (v1.34.1), SummarizedExperiment (v1.4.0), edgeR (v3.16.5), limma (v3.30.7), sva (v3.22.0), EnrichedHeatmap (v1.4.0), mgcv (v1.8-23), Picard (v2.2.2), seqtk (v1.2-r94), Salmon (v0.7.2), tximport (v1.2.0), Metascape (http://metascape.org), GREAT (v3.0.0; http://great.stanford.edu)

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

Raw and processed data generated are available through NCBI GEO under accession number GSE96615. [Reviewer link for GEO: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE96615.]
Processed data is available through a UCSC hub, at http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&hubUrl=https://s3.us-east-2.amazonaws.com/brainepigenome/hub.txt.

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 sample size calculation was performed; we chose 3 males and 3 females to allow the possibility of a segregation by sex.
Data exclusions	No data were excluded.
Replication	We did not replicate. We do have limited within sample replication as some of the same samples were analyzed using WGBS, RNA-seq and/or ATAC seq.
Randomization	Randomization was performed at the level of library preparation. There was no intervention so randomization was not employed in that sense.
Blinding	The analysts were not blinded.

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	The human brain tissues used in this study were obtained from the NIH Neurobiobank and while these exact tissues no longer exist, similar tissues can be made available by request to the tissue bank.

Antibodies

Antibodies used	For FANS we used anti-NeuN conjugated to AlexaFluor488 (cat. no. MAB377X, Millipore).

Validation	From the Manufacturer: Vertebrate neuron-specific nuclear protein called NeuN (Neuronal Nuclei). MAB377X reacts with most neuronal cell types throughout the nervous system of mice including cerebellum, cerebral cortex, hippocampus, thalamus, spinal cord and neurons in the peripheral nervous system including dorsal root ganglia, sympathetic chain ganglia and enteric ganglia. The immunohistochemical staining is primarily in the nucleus of the neurons with lighter staining in the cytoplasm. The few cell types not reactive with MAB377X include Purkinje, mitral and photoreceptor cells. Developmentally, immunoreactivity is first observed shortly after neurons have become postmitotic, no staining has been observed in proliferative zones. The antibody is an excellent marker for neurons in primary cultures and in retinoic acid-stimulated P19 cells. It is also useful for identifying neurons in transplants.Rat and mouse. It is expected that the Alexa Fluor® 488 conjugated antibody will also react with human, ferret, chick and salamander. Reference using on human and mouse tissues: Lister et al. Science (2013) 9;341 PMID: 23828890

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	A total of 2 × 250 mg of frozen tissue per sample was homogenized in 5 mL of lysis buffer (0.32 M sucrose, 10 mM Tris pH 8.0, 5 mM CaCl2, 3 mM Mg acetate, 1 mM DTT, 0.1 mM EDTA, 0.1% Triton X-100) by douncing 50 times in a 40 mL dounce homogenizer. Lysates were combined and transferred to a 38 mL ultracentrifugation tube and 18 mL of sucrose solution (1.8 M sucrose, 10 mM Tris pH 8.0, 3 mM Mg acetate, 1 mM DTT) was dispensed to the bottom of the tube. The samples were then centrifuged at 28,600 rpm for 2 h at 4C (Beckman Optima XE-90; SW32 Ti rotor). After centrifugation, the supernatant was removed by aspiration and the nuclear pellet was resuspended in 500 uL staining mix (2% normal goat serum, 0.1% BSA, 1:500 anti-NeuN conjugated to AlexaFluor488 (Millipore, cat#: MAB377X) in PBS) and incubated on ice. Unstained nuclei and nuclei stained with only secondary antibody served as negative controls.
Instrument	Beckman Coulter MoFlo Legacy Cell Sorter FL2 = PE
Software	Summit v4.3.02 Build 2451
Cell population abundance	The abundance of NeuN+ and NeuN- nuclei varied substantially from sample to sample and is in fact a main finding of our study. This is detailed in Supplementary Figure 1c. A small portion of the NeuN+ and NeuN- nuclei were re-run on the sorter to validate the purity which was greater than 95%.
Gating strategy	From the scatterplots in SuppFig1a, FS/SS events represent morphology of nuclei gated with debris excluded, doublets were excluded based on pulse width measurement. Gates for NeuN+ and NeuN- nuclei were set based on NeuN-488 staining intensity visualized by a histogram depicted in the representative example.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.