nature portfolio

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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	BD FACSdivca 8.0.1 , ImageJ (version 1.51).
Data analysis	Tools and R packages used: BEDTools 2.25.0, bedGraphToBigwig 4.0.0, ChIPSeeker 1.18.0, dTangle v2.0.9, edgeR 3.22.3, fastqc 0.11.2, GATK 3.5.0, GenomicFeatures 1.14.8, HiC-Pro 3.0.0, Juicer / HiCCUPS 1.6, LDSC 1.0.1, limma v4.1, MACS 2.1, PEER 1.3, PICARD 2.2.4, phantompeakqualtools 2.0, plink 1.90,QTLtools 1.3.1, R 3.5.3, RSubread 1.22.0, samtools 0.1.19, bwa -0.7.8-r455,Trimmomatic 0.36, variancePartition 1.17.9 All software are freely available.

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

Raw (FASTQ files) and processed data (peaks, differential analysis and CRD coordinates) have been deposited in synapse under synID syn25705564 (https://www.synapse.org/#!Synapse:syn25796149)

Browsable UCSC genome browser tracks of our processed ChIP-seq data are available as a resource http://genome.ucsc.edu/s/girdhk01/EpiDiff_Phase2

External validation sets used in the study are: H3K27ac ChIP-seq fetal specific peaks: Spatio-temporal enrichment of H3K27ac peaks table from http://development.psychencode.org/#, RoadMap Epigenome Project (REP) H3K27ac, H3K4me3 tissue ChipSeq peaks, chromHMM states on E073 and fetal male E081 and fetal female E082 https://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/coreMarks/jointModel/final/ and CTCF ChIPseq on human neural cell (GEO GSE127577). TruSeq3-PE.fa file was downloaded from the adaptor folder under the trimmotic repository. https://github.com/timflutre/ trimmomatic/blob/master/adapters/TruSeq3-PE.fa

The source data described in this manuscript are available via the PsychENCODE Knowledge Portal (https://psychencode.synapse.org/). The PsychENCODE Knowledge Portal is a platform for accessing data, analyses, and tools generated through grants funded by the National Institute of Mental Health (NIMH) PsychENCODE program. Data is available for general research use according to the following requirements for data access and data attribution: (https://psychencode.synapse.org/DataAccess).

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

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. Sequencing was done aon all available brains (N=739) from the Common Minds Consortium
Data exclusions	We excluded overall ~5% (N=37 out of 739) of the samples based on ENCODE quality controls metrics and sample outliers test using PCA plot.
Replication	We profiled H3K27ac from bulk tissue homogenate generated from N=249 (133 Control, 68 SCZ, 48 BD) samples as a replication dataset. All the findings were tested using statistical methods and were adjusted for multiple testing, either using Bonferroni or FDR.
Randomization	To avoid batch effects and other confounds, samples underwent repeated rounds of randomization, including (i) chromatin immunoprecipitation procedures and (ii) library preparation.
Blinding	Blinding was not relevant to this study, analysts were aware of data generation, processing and donor metadata.

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

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☐	☒ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	antihistone antibodies: anti-H3K4me3 (Cat# 9751BC, lot 7; Cell Signaling, Danvers, MA) and anti-H3K27ac (Cat# 39133, Lot# 31814008; Active Motif, Carlsbad, CA). See detailed description of the protocol (PMID:27113501) that includes details on dot blot with synthetic peptides and other QC.
Validation	Specificity was checked with histone H3 peptide array (Cat# 16-667; Millipore). Anti-NeuN-Alexa488 (Cat# MAB377X, EMD Millipore) antibody to stain nuclei, specificity was checked by microscopy. Quality controls for FACS-sorted nuclei were described in Kundakovic, M. et al. Practical Guidelines for High-Resolution Epigenomic Profiling of Nucleosomal Histones in Postmortem Human Brain Tissue. Biol. Psychiatry 81, 162–170 (2017).

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	Raw (FASTQ files) and processed data (peaks, differential analysis and CRD coordinates) have been deposited in synapse under synID syn25705564 (https://www.synapse.org/#!Synapse:syn25705564)
Files in database submission	Raw data(FASTQ) and Processed data(H3K4me3 NeuN+ peaks, H3K27ac NeuN+ peaks, H3K27ac-Tissue peaks BED files)
Genome browser session (e.g. UCSC)	Browsable UCSC genome browser tracks of our processed ChIP-seq data are available as a resource http://genome.ucsc.edu/s/girdhk01/EpiDiff_Phase2

Methodology

Replicates	We generate H3K27ac=249 from bulk tissue.
Sequencing depth	median of sequencing depth is 59 million mapped paired-end reads
Antibodies	antihistone antibodies: anti-H3K27ac (Cat# 39133, Lot# 31814008; Active Motif, Carlsbad, CA)
Peak calling parameters	narrow: macs2 Poisson p-value = 0.01 with --keep-dup all --nomodel --extsize = 150, Broad: macs2 P-value cutoff = .01, --extsize = 150.
Data quality	We used encode quality metrics like RSC(>1.0), NSC (>1.0) and NRF(>)0.8) to ensure data quality of samples.
Software	Alignment of FASTQ files:Burrows-Wheeler Aligner Filtering of bam files: Picard, samtools QC parameters: SPP, phantompeakcall Peak calling and quantifying chip-seq counts in peaks: macs2, bedtools, featureCounts Covariate Analysis: variancePartition +BIC Peak annotation: CHIPseeker Differential modification analysis: R (libraries: edgeR, diffbind) CRD calling: Decorate genetics enrichment analysis: LDSc heritability

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	Nuclei extraction from approximately 300mg aliquots of frozen prefrontal cortex tissue, immunotagging with NeuN antibody for subsequent fluorescence-activated nuclei sorting, chromatin digestion of sorted nuclei with micrococcal nuclease and subsequent pulldown with anti-H3K27ac and anti-H3K4me3 antibodies, library preparation and sequencing.
Instrument	FACSAria [BD Biosciences]
Software	BD FACSDiva Software
Cell population abundance	We report in the Methods section that for each cell type, a minimum of 400,000 nuclei was required as starting material.
Gating strategy	Separation of NeuN+ and NeuN- nuclei in FITC-A and Texas-Red (from DAPI-A), with windows picked to maximize specificity.

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