Corresponding author(s): Schahram Akbarian
Panos Roussos
Gabriel Hoffman

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	Postmortem brain tissue was provided by the HBCC at the National Institute of Mental Health, tissue is available to investigators compliant with NIH and HBCC rules and regulations . Antibodies and all other reagents were commercially available.
Data analysis	R, bedtools, samtools, ngsplot, picard, macs2, SPP, PeakSeq, variancePartition, GREAT, ChIPSeeker v.1.8.9

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

Data Availability Statement for the current study
The data analyzed for this article is available through the psychENCODE Knowledge Portal (psychencode.org). Access to the data is controlled by the NIMH Repository and Genomics Resources (NRGR) https://www.nimhgenetics.org. See instructions for in the PsychENCODE Knowledge Portal: https://www.synapse.org/#!Synapse:syn4921369. Data and results are at https://www.synapse.org/#!Synapse:syn4566010.

The site includes link to UCSC browser visualizations.
http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=chr21%3A34442450-34444728&hgsid=646126819_KMbat9BTznjd98mdtgzpJeyaDgEh

http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=chr5%3A149599054-149669403&hgsid=646126975_xg65uD60QPZDfbfowg7QwHMv5YYy

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	We generated 157 ChIP-Seq profiles on 36 subjects. ChIP-Seq was performed on neuronal, non-neuronal cells in PFC and ACC brain regions and homogenates in PFC brain region for H3K4me3 and H3K27ac histone marks. The sample size for cell type data on two brain regions for two histone marks is the largest available. Previously published pilot studies (Cheung,Shulha et al. , Proc Natl Acad Sci U S A. 2010 May 11;107(19):8824-9) conducted with only 10-12 samples implied strong cell type specific effects.
Data exclusions	8 Chip-Seq files were excluded after QCing on technical variables (see Table S2 and Methods)
Replication	Yes, all the findings were tested using statistical methods and were adjusted for multiple testing, either using Bonferroni or FDR.
Randomization	Approximately 300mg aliquots of frozen frontal (dorsolateral prefrontal and anterior cingulate gyrus) cortex tissue were obtained from control brains of the NIH Human Brain Collection Core (HBCC) (Director: Dr. Barbara K Lipska), cases were selected based on (i) no history of neurological or psychiatric illness , (ii) adult age, (iii) absence of agonal state before death and (iv) sufficient amounts of tissue available. To avoid batch effects and other confounds, samples underwent repeated rounds of randomization, including for the (i) chromatin immunoprecipitation procedures and (ii) library preparation.
Blinding	Blinding was not relevant in this study which is focused on histone mapping in reference brains No clinical samples were analyzed.

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: ANTIBODIES AND REAGENTS ARE COMMERCIALLY AVAILABLE. POSTMORTEM BRAIN SPECIMENS COULD BE REQUESTED FROM THE HUMAN BRAIN COLLECTION CORE (HBCC), a brain and tissue repository at the National Institutes of Mental Health.

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).

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.

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.

psychencode.org
http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=chr21%3A34442450-34444728&hgsid=646126819_KMbat9BTznjd98mdtgzpJeyaDgEh
http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=chr5%3A149599054-149669403&hgsid=646126975_xg65uD60QPZDfbfowg7QwHMv5YYy

Files in database submission: 1) BAM and BED with metadata files, 2) counts per million matrix of all individuals and list of significant peaks from differential modification analysis

Genome browser session
(e.g. UCSC): no longer applicable

Methodology

Replicates: not applicable, postmortem brain

Sequencing depth: We have used paired end reads, where length of the each read is 100 bp for cell type data and 75 bp for homogenate data. Table S2 lists the number of uniquely mapped reads.

Antibodies: antihistone antibodies: anti-H3K4me3 (Cat# 9751BC, lot 7; Cell Signaling, Danvers, MA) and anti-H3K27ac (Cat# 39133, Lot# 31814008; Active Motif, Carlsbad, CA).

Peak calling parameters: narrow peak: macs2 callpeak -t mergedBAMfile -c mergedinputfile --keep-dup all -f BAM -g hs -n oututfile --nomodel --extsize 150 -p 0.1

broad peaks: macs2 callpeak -t mergedBAMfile -c mergedinputfile --keep-dup all -f BAM -g hs -n outputfile --broad --broad-cutoff 0.1 --nomodel --extsize 150 -p 0.1

Data quality: ENCODE QC metrics: uniquely mapped reads, PBC, NSC, RSC, IDR
5% FDR

	Cell Specific H3K4me3:23838 (neurons), 31790 (non-neurons) H3K27ac:59,588 (neurons), 58,120 (non-neurons) Region Specific H3K4me3:696 (PFC in neurons), 508 (ACC in neurons) H3K27ac:10,665 (PFC in neurons), 10,797 (ACC in neurons) H3K4me3: 9 (ACC in non-neurons) H3K27ac:18 (ACC in non-neurons)
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 Peak annotation: CHIPseeker Differential modification analysis: R (libraries: edgeR, diffbind) Visualization data: ngsplot, R(libraries: ggplot2) Pathway enrichment analysis: GREAT

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 fluorescenceactivated 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. We illustrate the gating strategy in Figure S19 of the paper.

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