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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<br>*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<br>*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 | No software was use for Data collection |
| Data analysis | All software used for data analysis is available on GitHub: https://github.com/mjgirgenti/PTSDsnDLPFC and on Zenodo (https://doi.org/10.5281/zenodo.15186498)<br>10x Genomics Cell Ranger (v6.1.1): generate count matrix for RNA-seq data<br>CellBender (v0.2.2): remove technical artifacts from RNA-seq data<br>Scrublet (v0.2.3) and DoubletDetection (v4.2): remove doublets from each sample<br>Pegasus (v1.5.0): primary analysis tool for RNA-seq data<br>MAST (v1.21.3): DEG analysis tool<br>Wilcoxon in Seurat (v5.2.1): DEG analysis tool<br>Nebula (v1.5.3): DEG analysis tool that corrects sample bias<br>DESeq2 (v1.46.0): pseudobulk DEG analysis tool<br>EnrichR (v3.4): gene ontology enrichment tool<br>scCODA (v0.1.9): differential abundance analysis<br>RRHO (v1.46.0): threshold-free comparison of PTSD and MDD DEGs<br>CellChat (v1.5.0): cell-to-cell communication analysis<br>NeuronChat (v1.1.0): neural-specific cell-to-cell communication analysis<br>10x Genomics Cell Ranger ATAC (v2.0.0): generate peak count matrix for ATAC-seq data<br>ArchR (v1.0.2): primary analysis tool for ATAC-seq data<br>MACS2 (v2.2.9.1): calling peaks<br>Bedtools (v2.31.0): tool for genome arithmetic |

chromVAR (v1.28.0): calculate TF motif enrichment
igraph (v1.2.6): plot TF-CRE-Gene gene regulatory network
LDSC (v1.0.1): estimate heritability of traits
SuSiE (v0.12.35): variant fine-mapping statistical model
Juicer (v1.6): find TADs from HiC files
10x Genomics Cell Ranger ARC (v2.0.2): generate count matrix for Multiome data
Signac (v1.11.0): primary analysis tool for Multiome data
10x Genomics Xenium Ranger (v2.0): resegment nuclei boundaries
Squidpy (v1.6.1): primary analysis tool for Xenium data
SpatialData (v0.1.2): visualize Xenium slides

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

snRNA-seq, snATAC, and snMultiome count data count data generated and/or analyzed during the current study are available at https://doi.org/10.5281/zenodo.15186498.

We downloaded the following public datasets: Bulk DEGs: https://doi.org/10.1038/s41593-020-00748-7
Chatzinkos DEGs: https://doi.org/10.1176/appi.ajp.20220478
bCREs: https://psychscreen.wenglab.org/psychscreen/downloads
PTSD GWAS summary statistics: https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001672.v1.p1.
1000 Genomes Project (1KG) Phase 3 dataset: cog-genomics.org
NeuN+ HiC file: https://psychscreen.wenglab.org/psychscreen/downloads

## 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 | Our study was evenly powered for males and females across all -omics data including snRNA, snATAC and snMultiome sequencing. No sex-specific findings are reported in the manuscript |
| Reporting on race, ethnicity, or other socially relevant groupings | >90% of our cohort is Caucasian and the remaining are African, Asian and Hispanic American. All demographics for ancestry are included in Extended Data Figure 1 and Supplementary Table 1. |
| Population characteristics | This group includes donors with PTSD, MDD and neurotypical controls with no history of psychiatric disorder. Full demographics are provided in Extended Data Figure 1 and Supplementary Table 1 includes demographics for all donors. All analyses included covariate correction for common confounders (see Methods). The list of covariates are sex, ancestry, age, PMI, RIN, smoking, and antidepressant usage. |
| Recruitment | N/A |
| Ethics oversight | This project was approved by the Yale University 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

# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Sample size | While difficult to predict power in these studies when effect sizes are indeterminate. No explicit calculations were performed to determine |

| | |
|---|---|
| Sample size | sample size. We aimed to analyze brain tissue from approximately equal numbers of men and women across all three cohorts. There are ~ 35 donors across each cohort. We stress that most human postmortem brain genomics studies from previous publications include less than 30 donors. |
| Data exclusions | We removed 6 snRNA-seq and 8 snATAC-seq samples for low quality of sequencing. |
| Replication | There are currently no other sources of PTSD postmortem tissue and thus a replication cohort was not possible to include in the current study. |
| Randomization | Samples were organized by diagnosis: PTSD, MDD, or health control. Relevant covariates for postmortem genomics studies such as sex, ancestry, age, PMI, RIN, smoking and antidepressant use were corrected for. |
| Blinding | Data collection and analyses were not performed blind to tissue of origin but randomization was performed at the library preparation and sequencing stage. The final measurements of snRNA and snATAC are objective, relying on standardized compuational methods reducing the potential for bias. |

# 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 |
| ☒ | ☐ Clinical data |
| ☒ | ☐ Dual use research of concern |
| ☒ | ☐ Plants |

## Methods

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

## Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

| | |
|---|---|
| Cell line source(s) | NSB553-S1-1, male, European ancestry; NSB2607-1-4, male, European ancestry from the NIMH. |
| Authentication | All fibroblast samples were genotyped by IlluminaOmni 2.5 bead chip genotyping, PsychChip 129 , and exome sequencing. Parental hiPSCs were validated by G-banded karyotyping (Wicell Cytogenetics), with ongoing genome stability monitored by Infinium Global Screening Array v3.0 (Illumina) |
| Mycoplasma contamination | No mycoplasma detected |
| Commonly misidentified lines (See ICLAC register) | N/A |

## 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 | mus musculus, Strain #:013044 RRID:IMSR_JAX:013044, 8-10 weeks old. All mice were provided with food and water ad libitum and group-housed in a room maintained on a 12-hour light/dark cycle (7am to 7pm) at 72°F with 45% humidity. |
| Wild animals | No wild animals were used in this study. |
| Reporting on sex | males and females were used. N= 16 males and N= 15 females. no sex based analyses were performed. |
| Field-collected samples | No field collected samples were used in this study. |
| Ethics oversight | All animal experiments were approved by the Institutional Animal Care and Use Committee of Yale University School of Medicine (protocol 2024-20430). |

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 | NA |
| Authentication | NA |