ery with cell type-specific functional genomic data, single-cell multiomics is poised to advance our understanding of the neurobiology of psychiatric disorders and ultimately advance therapeutic development. However, analyzing these data poses unique challenges including their sparsity, technical noise, and high dimensionality. This session will highlight cutting-edge analytical frameworks—including non-parametric models, developmental trajectory mapping, and multicellular network inference—that address these barriers to decode disease biology. Speakers will demonstrate how integrating GWAS findings with single-cell data holds potential to prioritize regulatory circuits driving neurodevelopmental divergence and identify disease-relevant cell types.

Disclosure: Nothing to disclose. (Pouget, Lynall, Bicks)

doi: 10.1016/j.euroneuro.2025.08.506

MAPPING CELL TYPE-SPECIFIC EPIGENETIC REGULATION IN DORSOLATERAL PREFRONTAL CORTEX (DLPFC) TO UNCOVER MOLECULAR MECHANISMS IN PSYCHIATRIC DISORDERS

Jennie Pouget

Centre for Addiction and Mental Health

Psychiatric disorders have a strong genetic basis, with GWAS implicating hundreds of loci. Most of these GWAS variants are non-coding, and likely influence disease by altering gene expression in specific neuronal and glial cell types. Existing bulk tissue studies obscure cell type-specific gene regulation, making disease mechanisms difficult to parse. Leveraging advances in multimodal single-cell technologies, we developed robust cell type-specific maps of epigenetic regulation in DLPFC. Our enhancer-gene maps can be leveraged to understand epigenetic regulation in the brain, and uncover molecular mechanisms underlying GWAS loci.

We analyzed >170,000 cells from postmortem DLPFC tissue from neurotypical individuals spanning developmental timepoints from fetus to adulthood. All cells had paired multiomic measurements of enhancer activity (sn-ATACseq) and gene expression (sn-RNAseq) using the 10x Genomics Multiome protocol. We used SCENT, a novel non-parametric bootstrapping enhancer-gene mapping method, to link ATAC peaks (putative enhancers) with gene expression (target genes) in six major brain cell types: inhibitory neurons, excitatory neurons, astrocytes, microglia, oligodendrocytes, and oligodendrocyte precursor cells (OPCs).

Among >1.2M possible enhancer-gene pairs, we identified >14k putative enhancer-gene links (FDR < 0.10). Our enhancer-gene maps uncovered putative cell type-specific mechanisms underlying known psychiatric disorder GWAS loci, often resolving a single high-confidence variant. To validate our findings, we are evaluating whether these putative causal variants prioritized by SCENT influence chromatin accessibility in an allele-specific manner using matched genotype and sn-ATACseq data. These analyses could provide orthogonal support that SCENT peaks capture biologically meaningful regulatory variation. Overall, our multiomic single-cell resolution approach demonstrates potential to improve fine-mapping of GWAS loci by pinpointing what genes are dysregulated in psychiatric disorders, and in which specific cell types.

Disclosure: Nothing to disclose.

doi: 10.1016/j.euroneuro.2025.08.507

TRANSCRIPTOMIC AND CHROMATIN DYNAMICS OF THE HUMAN PTSD BRAIN AT SINGLE CELL RESOLUTION

Matthew Girgenti [1], Ahyeon Hwang [2], Mario Skarica [1], Jing Zhang [2], Siwei Xu [2], Jensine Coudriet [1], Alexa-Nicole Sliby [1], Jiawei Wang [1], Dianne Cruz [3], Douglas Williamson [3], Alicia Che [1], Hongyu Zhao [4], Keith Young [5], John Krystal [1]

[1] *Yale School of Medicine;* [2] *University of California Irvine;* [3] *Duke University Medical Center;* [4] *Yale School of Public Health;* [5] *Texas A&M University College of Medicine*

Post-traumatic stress disorder is a multigenic disorder occurring in the aftermath of severe trauma exposure. We isolated >2M nuclei from human postmortem dorsolateral prefrontal cortex from cases and controls for single nucleus(sn) RNA sequencing across three diagnostic cohorts: PTSD, major depression (Psychiatric control), and neurotypical controls to identify neuronal and non-neuronal cell type clusters and cell type-specific gene expression changes (DEGs). We then performed paired sn-sequencing of the same samples for ATAC-sequencing, to measure chromatin accessibility. In addition, we validated our transcriptomic findings by performing single cell, spatial transcriptomics on a subset of donors using the Xenium platform. We identified 14 distinct cell type clusters including neuronal and non-neuronal cell types. We identified over 1142 FDR significant DEGs across many cell types and confirmed expression changes of several genes implicated in PTSD pathophysiology by spatial transcriptomics. We found PTSD specific cis-regulatory elements for several genes including ELFN1, FKBP5, and KCNIP4. We also identified disease-specific receptor-ligand communication pattern disruption between cell types of the DLPFC. We constructed the gene expression regulatory landscape of PTSD by integrating RNA and ATAC modalities to define cis-regulatory elements (CREs) and transcription factor regulatory networks and linked these to DEGs. This enabled us to fine-map all of the PTSD GWAS risk genes from the Million Veteran Program into specific cell types. We discovered selective changes in the glucocorticoid system (long implicated in PTSD pathology) that were surprisingly most pronounced in endothelial cells and to a lesser extent other non-neuronal cells. In addition, we identify vulnerability of somatostatin (SST) interneurons in PTSD and global shifts in the transcriptome reflecting decreases in SST signaling and neurotransmission. These changes are accompanied by decreased output of microglia signaling suggesting suppression of neuroimmune mechanisms in the PTSD PFC. Overall, this work enabled characterization of gene pathways and their dynamics in diverse cortical cell types and prediction

of cis-regulatory logic and associated factors underpinning the molecular etiology of PTSD.

Disclosure: Nothing to disclose.

doi: 10.1016/j.euroneuro.2025.08.508

SINGLE-CELL MULTIOMIC APPROACHES FOR UNDERSTANDING HUMAN BRAIN VARIABILITY IN HEALTH AND DISEASE

Margarita Behrens

The Salk Institute

Diversity and individual variability are essential to human cognitive function. Identifying the conserved and variable transcriptomic and epigenomic signatures of the brain's cellular components is critical for understanding the neurobiological basis of individual variation and how this changes with age and in mental disorders. We will discuss results from a multiomic single-cell epigenome and transcriptome analyses performed on brain samples with sex and age diversity, and show they provide new insight into the diversity of brain-cell molecular identity across individuals. As well, we will discuss age-related changes in the epigenome of specific cell-types in relation to neurological disorders.

Disclosure: Nothing to disclose.

doi: 10.1016/j.euroneuro.2025.08.509

DEVELOPMENTAL ORIGINS OF PSYCHIATRIC RISK: DISSECTING GENE REGULATION THROUGH SINGLE-CELL MULTIOMIC ANALYSIS

Panos Roussos

Icahn School of Medicine at Mount Sinai

Psychiatric disorders such as schizophrenia, bipolar disorder, major depression, and autism spectrum disorder frequently originate from disruptions in neurodevelopmental processes, many of which unfold long before clinical symptoms emerge. However, dissecting the molecular and regulatory mechanisms that underlie these early developmental perturbations has remained a major challenge, particularly due to limited access to human brain tissue across the lifespan and the complexity of brain cellular diversity.

To address this, we applied state-of-the-art single-nucleus multi-omic technologies—simultaneously profiling gene expression and chromatin accessibility—to construct high-resolution atlases spanning key stages of human brain development and adulthood. Our datasets encompass over one million nuclei from multiple brain regions, including the dorsolateral prefrontal cortex (DLPFC), a region central to cognition and psychiatric vulnerability, and the olfactory epithelium (OE), a regenerative sensory tissue with neurogenic potential. These integrative datasets enable unprecedented insights into dynamic transcriptional programs and epigenetic regulation during neurodevelopment and aging.

Through trajectory inference and enhancer-gene regulatory network reconstruction, we identified stage-specific transcription factors and cell-type-specific cis-regulatory modules that guide neuronal and glial lineage commitment. We discovered striking convergence in gene regulatory dynamics between olfactory sensory neuron development and early-stage cortical excitatory neurons, suggesting that the OE may serve as a surrogate system to model human neurodevelopment. Furthermore, integrating our regulatory maps with genome-wide association study (GWAS) loci for major psychiatric disorders allowed us to prioritize putative causal genes and regulatory elements operating at specific developmental windows.

Collectively, our findings highlight the power of multiomic single-cell analysis in unraveling the developmental origins of psychiatric disease. By linking genetic risk to temporally defined regulatory programs and accessible cell types, this work lays a foundation for future efforts to pinpoint disease mechanisms and therapeutic targets. Moreover, our demonstration that accessible neurogenic tissues can recapitulate key features of brain development opens new avenues for modeling psychiatric risk in vivo.

Disclosure: Nothing to disclose.

doi: 10.1016/j.euroneuro.2025.08.510

ENHANCED MECHANISTIC INSIGHTS AND PREDICTIONS THROUGH INTEGRATING GENETICS AND NEUROIMAGING IN PSYCHIATRY

Ole Andreassen, Chair[1], Carolina Makowski, Co-chair[2], Jakub Kopal, Discussant[3]

[1] *University of Oslo;* [2] *University of California San Diego;* [3] *Centre for Precision Psychiatry, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo*

Overall Abstract: To accomplish a comprehensive understanding of complex psychiatric disorders, a multimodal approach is required. Alterations in brain structure and function sit along the causal continuum from genetic variants to behavioural symptoms defining psychiatric disorders. Combining neuroimaging and genetics can expand our understanding of the underlying mechanisms and pathophysiology of psychiatric disorders. The knowledge gained from such multimodal investigations has the potential to inform clinical translation of psychiatric genomics findings.

This symposium will include four presentations of frontline research which incorporate common or rare genetic variants in conjunction with brain imaging. To understand and leverage the underlying biology of psychiatric disorders, the speakers use multimodal approaches and novel analytical tools. Each presentation will illustrate how integrating data from psychiatry, genetics, and neuroimaging can enhance genomic discoveries, advance mechanistic insights, and improve prediction and/or patient stratification.

Dr. Pravesh Parekh will introduce the FEMA-GWAS tool and show results from its application on charting the genetic variants associated with longitudinal changes in brain development, using data from the Adolescent Brain Cognitive