An integrated multi-omics dissection of PTSD and MDD across brain regions and cell types

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The gene-regulatory landscape of the brain is highly dynamic in health and disease, coordinating many biological processes across distinct cell types. The neurobiology of PTSD and major depressive disorder (MDD) regarding stress-associated genetic, epigenetic, and transcriptional mechanisms is increasingly understood, yet many critical questions remain. Recent developments including the creation of large scale GWAS consortia to identify genetic variants associated with increased risk for PTSD and MDD require postmortem human brain tissue to elucidate the molecular biological mechanisms involved. Here we generated the largest multi-omic postmortem database of PTSD and MDD compared to neurotypical controls that includes RNA expression, DNA methylation, and protein expression from the dorsolateral prefrontal cortex, amygdala and the hippocampus. Single nucleus RNA-seq data was generated to infer cell-type-specific expression. Multi-omics integration identified pathways including glucocorticoid signaling, GABAergic transmission, and inflammation as differentially enriched in PTSD and MDD. At RNA and methylation levels, there was an aggregation of differential expression in specific PTSD risk loci including CRHR1, ELFN1, and MAD1L1. Overall, the identified associations point to genetic, epigenetic, and cell type-specific related mechanism of brain pathophysiology in PTSD and MDD and indicate several novel promising biomarkers and therapeutic targets.

1. Wang J, …, Girgenti MJ. Posttraumatic Stress Disorder Brain Transcriptomics: Convergent Genomic Signatures Across Biological Sex. **Biol Psychiatry** S0006-3223(21)00116-5, Epub ahead of print (2021).
2. Stein MB, …, Girgenti MJ, …, Gelernter J. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. **Nat Genet** 53(2):174-184 (2021).
3. Girgenti MJ, …, Duman RS. Transcriptomic organization of the human brain in post-traumatic stress disorder. **Nat Neurosci** 24, 24-33 (2021).