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Using Single Cell Multiomics to Discover Novel Factors in the Brain Involved in Co-Occuring Opioid Addiction and Major Depression

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The opioid epidemic constitutes a critical public health crisis marked by overdose fatalities and devastating relapse rates in those seeking recovery from opioid use disorder (OUD). Comorbidity with major depressive disorder (MDD) occurs in ~36% of OUD cases, exacerbating adverse outcomes. Despite shared genetic risk loci identified between OUD and MDD, cell-type-specific molecular mechanisms underlying these disorders and their comorbidity remain poorly understood. Emerging evidence indicates that opioid exposure induces transcriptomic changes in glial cells, affecting genes involved in immune responses and neuronal communication. Alterations in astrocytic μ-opioid receptor expression and gliotransmitter release have been linked to reward processing, withdrawal, and depressive-like behaviors, underscoring glia's involvement in the pathophysiology of OUD and MDD. Despite this, previous work largely overlooks glia in favor of neurons. We hypothesize that glial cell types will exhibit altered gene expression and regulatory network dynamics in postmortem human brain tissues from individuals diagnosed with OUD, MDD, and comorbid OUD/MDD, as compared to unaffected controls. To test this, we employed advanced single-nucleus RNA sequencing and assay for transposase-accessible chromatin sequencing using the 10x Genomics Multiome assay. Focusing on the nucleus accumbens—a region implicated in both reward and motivation—we identified cell type-specific transcriptional and epigenetic alterations across diagnostic groups. This study reports novel glia-specific pathways differentially active across OUD and MDD cohorts and in comorbidity. Understanding these cell-type-specific alterations is essential for developing novel precision therapeutics to mitigate the substantial public health impact of these disorders.