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Unique epigenomic and transcriptional signatures in co-occurring opioid use disorder and major depressive disorder in human cortex

Opioid use disorder (OUD) and major depressive disorder (MDD) frequently co-occur, yet the cell-type-specific regulatory mechanisms underlying this comorbidity (COM) remain poorly understood. In individuals with OUD, MDD, COM, and unaffected individuals, we conducted single-nucleus multiome sequencing on the human subgenual anterior cingulate cortex (sgACC), a mood-related region implicated in both OUD and MDD. The crux of the study focused on whether COM individuals exhibited additive or synergistic pathology compared to individuals with only OUD or MDD. Integration of gene expression, chromatin accessibility, and peak-to-gene linkages revealed that individuals with COM exhibit minimal overlap with signatures of OUD or MDD alone. The most prominent neuronal alterations occurred in layer 6 corticothalamic excitatory neurons, showing reduced accessibility at intronic regulatory elements tied to synaptic vesicle cycling and calcium-dependent exocytosis. In contrast, RORB intratelencephalic neurons displayed increased distal enhancer accessibility enriched for metal homeostasis pathways. Regulon and motif analyses showed elevated activity-regulated AP-1 and immediate-early gene programs in COM relative to OUD, but attenuated compared to MDD, with subtype-specific shifts in stress- and chromatin-regulating factors. Intersection with GWAS prioritized candidates including GATAD2A, GRK4, ADD1, and SH3BP2. These findings highlight enhancer-compartment-specific, non-additive regulatory programs in sgACC as a hallmark of OUD/MDD comorbidity.

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