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Heroin abuse-associated transcriptional and epigenetic alterations in the orbitofrontal cortex concentrate in GABA interneurons and provide insight into potential sex-specific regulatory response

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Understanding the cell type-specific effects of heroin on chromatin accessibility and gene expression in brain regions controlling decision making can elucidate the biological effects of this potent drug of abuse. Here we generated transcriptomic (RNA-seq) and epigenomic (ATAC-seq) datasets in FACS-sorted nuclei from glutamatergic and GABAergic neurons and oligodendrocytes from autopsied orbitofrontal cortex, the region implicated in impulse control, goal-directed behaviors, as well as drug addiction. Tissue was collected from subjects who died of heroin overdose and controls (n = 30/cell type/condition) to assess heroin-specific (epi)-genomic responses. Complementary H3K27ac ChIP-seq data for 9 heroin and 9 control donors of the same cohort were also acquired. Differential expression (DE) analyses revealed that *PENK* and *POMC* were downregulated in GABAergic neurons, whereas multiple immediate early genes (e.g., *ARC* and *NPAS4*) were downregulated in glutamatergic and GABAergic neurons. Moreover, through multi-omic analyses we identified several cases of differential chromatin accessibility in or near genes demonstrating differential expression, including heroin-induced decreased accessibility in the TSS of *ADAMTS1* in oligodendrocytes that correlated with decreased gene expression. Furthermore, in GABAergic neurons we identified 69 genic or intergenic differential ATAC-seq peaks with the closest gene being identified as DE, including *PCSK1* and *VGF*. Notably, sex-specific differences were observed in regulatory regions associated with gene expression variation in heroin users. We highlight heroin-induced, sexually dimorphic effects in GABAergic interneurons in the promoter region of *SHC4*. Together, these novel tissue- and cell type-specific analyses identify important regulatory dynamics and gene expression changes resulting from heroin use.