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Multimodal RNA-sequencing of the dorsal striatum identifies a link between H3K27 dysregulation and neurodegenerative phenotypes in heroin use.

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Background: The dorsal striatum is a critical structure for the development of habitual and compulsive behaviors, but its molecular pathophysiology relevant to opioid use disorder remains understudied. *Rationale/Significance:* We conducted bulk RNA-sequencing of two dorsal striatal subregions and single-nucleus RNA-sequencing to discern subregion and cell-type specific transcriptional changes. *Hypothesis:* Our previous work identified striatal changes in H3K27 acetylation of genes related to synaptic plasticity, so we hypothesized that these alterations would be specific to medium spiny neurons (MSN), the major striatal cell-type. *Results:* Bioinformatic analyses revealed a network of genes regulated by the polycomb repressive complex 2 (PRC2) and involved in axon guidance upregulated in the posterior dorsomedial striatum. PRC2 is known to regulate H3K27 and MSN identity. Single-nucleus RNA-sequencing demonstrated a loss of MSN-specific marker expression. Notably, differentially expressed genes in neurons involved in neurodegenerative disorders following heroin self-administration recapitulated bulk RNA-sequencing striatal results from post-mortem human heroin users. The downregulation of MSN-specific markers was reproduced in a separate human single-nucleus RNA-seq dataset. Furthermore, administration of JQ1, a bromodomain inhibitor that blocks the functional readout of genes downstream of the loss of PRC2, reversed effects on genes in neurodegenerative pathways. *Discussion:* These results suggest volitional heroin use induces a neurodegenerative-like phenotype in the dorsal striatum through epigenetic mechanisms regulating the post-translational modification of histone H3K27. Implications include potential adverse neurocognitive consequences of chronic opioid use, highlighting the importance of non-opioid treatments for opioid use disorder while the molecular pathways and perturbations identified might serve as novel drug targets.