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Ex-Specific Chromatin and Transcriptional Signatures in Medial Prefrontal Cortex Following Heroin Exposures

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Opioid abuse impacts millions of Americans, resulting in tens of thousands of deaths annually. Relapse, often driven by heightened craving during abstinence, is linked to altered neuroplasticity. The medial prefrontal cortex (mPFC), a region responsible for executive function, plays a key role in drug-seeking behavior and relapse. To better understand the molecular changes that occur in mPFC to potentiate these behaviors, it is critical to understand how specific cell-types are affected. Thus, we performed single-nuclei multiomics, analyzing gene expression and chromatin accessibility in the same cells. Male and female rats were exposed to heroin using a fixed ratio schedule of reinforcement, with tissues collected after 14 days of abstinence (AD-14) or following volitional re-exposure to heroin in a progressive ratio (PR) task. Saline controls were also included. Significant changes in gene expression and chromatin accessibility were largely only observed in females, particularly within specific glutamatergic sub-types. Hundreds of genes involved in developmental processes, notably WNT signaling and synaptic regulation, were upregulated at AD-14 compared to saline controls. Following drug re-exposure, many of these same genes were oppositely regulated, suggesting a reversal of the transcriptional/chromatin signatures observed during abstinence. We are now working to link these transcriptional changes to alterations in chromatin accessibility, specifically within enhancer regions, to identify and experimentally validate potential therapeutic targets for preventing drug-seeking behavior and compulsive drug-taking during relapse.