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Epigenomic remodeling at single cell resolution in cocaine self-administration in mice

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Relapse to drug use is the major challenge in combating addiction. Central to this problem is post-withdrawal long-lasting changes in the brain that can persist for an extended period, which is associated with long-term changes in gene expressions and the epigenome. Drug-induced epigenomic changes have been studied in bulk preparations of mouse and human brain samples. However, these studies lack the resolution as to in which cell types the epigenomic remodeling occurs and how different aspects of the epigenome cooperatively regulate the gene expression. We hypothesize that the epigenomic remodeling in response to drug consumption is cell type-specific, and different cell types harbor different long lasting epigenomic alterations. To test this hypothesis, we use an interdisciplinary that combines the mouse model of intravenous self-administration (IVSA) of cocaine with single-cell epigenomics and multi-omics assays. In the pilot study, we analyzed the dynamic landscapes of chromatin accessibility and DNA methylation in nucleus accumbens (NAc) after cocaine IVSA and abstinence. We observed genome-wide epigenomic changes after cocaine IVSA, the majority of which were cell-type specific and were enriched at non-promoter cis-regulatory elements. In addition, some of these epigenomic alterations persisted during the abstinence, suggesting epigenetic regulations of long-lasting gene expression alteration in specific cell types. These ongoing studies will help illustrate cell type-specific epigenetic mechanisms in addiction, and provide crucial knowledge for follow-up targeted functional studies of key epigenomic regulators.