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A Single Cell Approach to Study Cocaine Use Disorder

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Cellular mechanisms underlying substance use disorders (SUDs) are incompletely understood. Intravenous self-administration (IVSA) procedures in rodents can recapitulate behavioral abnormalities often observed in people with SUDs, including drug consumption resistant to negative outcomes. Analysis of transcriptional responses to drugs of abuse in the brains of IVSA-experienced animals using bulk RNA-sequencing approaches has identified genes involved in SUD-related behaviors and also altered in humans with SUD. However, such approaches lack cellular specificity. Advances in single-nucleus RNA sequencing (snRNA-seq) can overcome this limitation by revealing cell type-specific transcriptomic responses to drugs of abuse. In particular, whole-brain snRNA-seq technologies could facilitate assessment of drug-induced transcriptional remodeling in a brain-wide unbiased manner. Here, we apply EasySci snRNA-seq to assess the cell type-specific transcriptional responses to cocaine IVSA across the brains of mice, with an emphasis on subcortical regions implicated in SUD-related behaviors (e.g., nucleus accumbens, dorsal striatum, habenula). Included were mice with short (1 h) or long (5 h) daily access to cocaine IVSA or saline-only control mice. Importantly, mice with long access to cocaine demonstrate punishment-resistant responding for the drug. We anticipate that EasySci unbiased transcriptional mapping approach will identify brain regions and cell types contained therein with robust transcriptional responses to long daily access to cocaine, which are potentially involved in compulsive cocaine-taking behavior. In these cells, we plan to define the chromatin landscape, interactions with regional cells, differential RNA splicing, correlation of polyadenylation with RNA binding proteins, and molecular effects of genetic variants predisposing humans to addiction.
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