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Development of multipleXed Population Selection and Enrichment single nuclei RNA-sequencing (XPoSE-seq) to characterize neuronal ensembles in cocaine relapse

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Relapse is an ongoing clinical problem, and there are currently no effective treatments to reduce the risk of relapse to psychostimulants like cocaine. Environmental stimuli previously associated with drug-taking can precipitate relapse long after cessation of drug use. These maladaptive cue-drug associations are hypothesized to be encoded within specific patterns of neurons (neuronal ensembles) that are selectively activated by drug-related cues. Our lab and others have shown causal roles for neuronal ensembles in reward-seeking behaviors and identified unique molecular and functional alterations within them. However, due to methodological limitations, previous studies could not characterize cell-type diversity of ensembles or identify molecular alterations within specific ensemble cell-types.

To address this gap, we developed a new Multiple**X**ed **Po**pulation **S**election and **E**nrichment **s**ingle **n**uclei RNA-**seq**uencing (XPoSE-seq) pipeline to determine cell-type composition of rare ensemble populations (<10% of neurons in a region) and define their transcriptional profiles following learned behaviors. We used XPoSE-seq to create a neuronal cell-type atlas of rat infralimbic cortex (IL), examined which IL cell-types are activated in male and female rats during novel context exploration, and characterized cell-type specific transcriptional responses within these ensembles. We found that IL novel context ensembles comprise multiple excitatory and inhibitory neuronal cell-types that have distinct transcriptional signatures. We will use XPoSE-seq to investigate cell-type diversity of IL cocaine-relapse ensembles and identify cell-type specific transcriptional signatures within these relapse-specific populations. In future studies, we will employ CRISPR-based transcriptional modulators to assess causal roles for identified cocaine memory-specific transcriptional fingerprints in persistent cocaine relapse during abstinence.