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Cell-type-specific transcriptional signatures of cocaine relapse in the rat medial prefrontal cortex

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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 Multiple**X**ed **Po**pulation **S**election and **E**nrichment single nuclei RNA**-seq**uencing (XPoSE-seq) to determine cell-type composition of rare ensemble populations and define their transcriptional profiles following cocaine relapse. We trained rats to self-administer cocaine during twice daily 3 h sessions. Following 21 days of abstinence, we tested rats for cocaine-seeking or no test control and collected brains 3 h after the test (peak ensemble marker expression). We isolated ensemble and non-ensemble neuronal nuclei as input for XPoSE-seq. Our analysis revealed distinct clusters corresponding to known cell types in the mPFC (excitatory and inhibitory neurons) that further subcluster into expected layer and interneuron sub-types within mPFC. Using this unbiased approach, ongoing analysis aims to characterize cell-type and ensemble-specific transcriptional signatures that contribute to drug seeking behaviors. Future work will manipulate key candidate genes and identify relevant circuits.