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Transcriptional profiling of cocaine relapse ensembles in the rat medial prefrontal cortex to inform drug repurposing strategies

Relapse is an ongoing clinical problem, and there are currently no effective treatments to reduce the risk of relapse to psychostimulants like cocaine. Environmental cues previously associated with drug-taking can provoke craving and cause relapse long after cessation of drug use. One strategy to combat relapse is to disrupt drug-cue associative memory by targeting molecular mechanisms that are selectively engaged in neuronal ensembles—populations of neurons activated during relapse-related behaviors. However, the cell types comprising relapse ensembles and how they maintain this association at the molecular level are unknown. To answer this question, we recently developed MultipleXed Population Selection and Enrichment single nucleus RNA-sequencing pipeline (XPoSE-seq) to perform targeted snRNA-seq on cocaine relapse ensembles, providing an unbiased screen of ensemble-specific cell types and transcriptional changes during cocaine relapse at the individual animal level.

Male and female Fos-mRFP rats were trained to self-administer cocaine (FR1 reinforcement schedule, 0.75 mg/kg/inf. cocaine paired with a 3.5-s light cue) during twice daily 3 h sessions. Following training and 21 days of abstinence, we tested rats for cocaine seeking (30 min, extinction conditions) and collected brains 3 h after test (peak Fos-driven mRFP expression). Rats show reliable cocaine self-administration during training and cocaine seeking following abstinence. We applied the XPoSE-seq pipeline to identify which cell types comprise the cocaine relapse ensemble and to characterize the associated cell-type specific transcriptional signatures. We identified 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. We used drug repurposing analysis on the transcriptional signatures to identify drugs with compensatory molecular changes, which identified 35 FDA-approved candidates. A subset of these drugs were tested for effects on food self-administration, and ongoing work is testing their impact on relapse to cocaine seeking in rats.

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