Leveraging single-cell profiling to identify drug-responsive genetic programs in brain reward circuitry

Jeremy J. Day

Drugs of abuse elevate dopamine levels in the nucleus accumbens (NAc) and alter transcriptional programs believed to promote long-lasting synaptic and behavioral adaptations. In this presentation, I will discuss our recent efforts leveraging single-nucleus RNA-sequencing (snRNA-seq) and Assay for Transposase Accessible Chromatin (snATAC-seq) to generate a comprehensive molecular atlas of cell subtypes in the NAc, defining both sex-specific and cell type-specific responses to acute and repeated drug experience in a rat model system. Our work demonstrates that psychostimulant drugs such as cocaine recruit activity-dependent transcriptional programs in the NAc to subsequently initiate chromatin reorganization at enhancer elements near genes implicated in synaptic function. Moreover, we show that direct activation of a core dopamine-driven gene program with a multiplexed CRISPR strategy initiates a secondary synapse-centric transcriptional profile, alters striatal physiology *in vitro*, and enhances cocaine sensitization *in vivo*. Taken together, these results define the genome-wide transcriptional response to cocaine with cellular precision, and highlight the mechanisms by which drugs of abuse initiate experience-dependent chromatin remodeling.

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