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Distinct subpopulations of D1 medium spiny neurons exhibit unique transcriptional responsiveness to cocaine

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Drugs of abuse increase extracellular concentrations of dopamine in the nucleus accumbens (NAc), resulting in transcriptional alterations that drive long-lasting cellular and behavioral adaptations. While decades of research have focused on the transcriptional mechanisms by which drugs of abuse influence neuronal physiology and function, few studies have comprehensively defined NAc cell type heterogeneity in transcriptional responses to drugs of abuse. Here, we used single nucleus RNA-seq (snRNA-seq) to characterize the transcriptome of over 39,000 NAc cells from male and female adult Sprague-Dawley rats following acute or repeated cocaine experience. This dataset identified 16 transcriptionally distinct cell populations, including two populations of medium spiny neurons (MSNs) that express the Drd1 dopamine receptor (D1-MSNs). Critically, while both populations expressed classic marker genes of D1-MSNs, only one population exhibited a robust transcriptional response to cocaine. Validation of population-selective transcripts using RNA in situ hybridization revealed distinct spatial compartmentalization of these D1-MSN populations within the NAc. Finally, analysis of published NAc snRNA-seq datasets from non-human primates and humans demonstrated conservation of MSN subtypes across rat and higher order mammals, and further highlighted cell-type transcriptional differences across the NAc and broader striatum. These results highlight the utility in using snRNA-seq to characterize both cell type heterogeneity and cell type-specific responses to cocaine and provides a useful resource for cross-species comparisons of NAc cell composition.