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A dopamine-induced gene expression signature regulates neuronal function and cocaine response

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Drug addiction is a worldwide health problem, with overdose rates of both psychostimulants and opioids currently on the rise in many developed countries. Drugs of abuse elevate dopamine levels in the nucleus accumbens (NAc) and alter transcriptional programs believed to promote long-lasting synaptic and behavioral adaptations. However, even with well-studied drugs such as cocaine, drug-induced transcriptional responses remain poorly understood due to the cellular heterogeneity of the NAc and complex drug actions via multiple neurotransmitter systems. Here, we leveraged high-throughput single-nucleus RNA-sequencing to create a comprehensive molecular atlas of cell subtypes in the NAc, defining both sex-specific and cell type-specific responses to acute cocaine experience in a rat model system. Using this transcriptional map, we identified specific neuronal subpopulations that are activated by cocaine, and defined an immediate early gene expression program that is upregulated following cocaine experience *in vivo* and dopamine (DA) receptor activation *in vitro*. To characterize the neuronal response to this DA-mediated gene expression signature, we engineered a large-scale CRISPR/dCas9 activation strategy to recreate this program. Multiplexed induction of this gene program initiated a secondary synapse-centric transcriptional profile, altered striatal physiology *in vitro*, and enhanced cocaine sensitization *in vivo*. Taken together, these results define the genome-wide transcriptional response to cocaine with cellular precision, and demonstrate that drug-responsive gene programs are sufficient to initiate both physiological and behavioral adaptations to drugs of abuse.