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Elucidating the cell type-specific transcriptional patterns differentiating stimulant versus opiate addiction

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The onset and persistence of drug addiction is, in part, effected via cell-type specific mechanisms of transcription in the brain. However, between classes of abusive drugs, little is known about the overlap of common transcriptional mechanisms and how these converge and diverge to effect an addictive phenotype. Within the nucleus accumbens (NAc), ΔFosB, a Fos family transcription factor, accumulates in D1 medium spiny neurons (MSNs) following repeated exposure to cocaine, but in both D1 and D2 MSNs after chronic morphine. This phenomenon makes ΔFosB and its downstream effectors promising therapeutic targets but it is unknown how ΔFosB coordinates the unique effects of stimulants and opiates. To determine the D1- vs D2-MSN specificity of ΔFosB targets, we adapted CRISPR/Cas9 technology to recapitulate drug-induced transcription when ΔFosB is induced in a MSN-specific manner and performed RNAseq. By inducing ΔFosB accumulation in the absence of drug, we addressed the whole-NAc transcriptional outcomes of ΔFosB's induction in D1- and/or D2-MSNs, and how these outcomes inform how different pharmacological substances alter transcription to commonly or divergently influence the function of the brain's reward system. Understanding the transcriptional scope and cell type-specific roles of ΔFosB in the effects of cocaine and morphine clarifies their mechanisms of action and reveals new avenues for therapeutic development. Moreover, our method for studying the genomic patterns coordinated by a single transcription factor more broadly serves as a novel mode of investigation into understanding how cell type-specific transcription and epigenetic patterns interact with environmental input to guide behavior.