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Cell subtype transcriptional programs in cocaine intake and seeking behavior

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We have previously reported the down regulated expression of a transcription factor, early growth response 3 (Egr3), in nucleus accumbens (NAc) dopamine receptor 2 expressing spiny projection neurons (D2-SPNs) with exposure to cocaine. Additionally, mice with Egr3 overexpression in NAc D2-SPNs have altered extinction of cocaine seeking behavior and drug-induced reinstatement after forced abstinence from cocaine self-administration. We found that the NGFI-A binding protein 2 (Nab2), a corepressor of Egr3, is altered in bidirectional manner to Egr3 in D2-SPNs of mice repeatedly exposed to cocaine. Using CRISPR epigenome editing approaches we observe that enhancing Nab2 transcription results in reduced Egr3 levels, and blunting Nab2 transcription promotes increased levels of Egr3. To further understand the functional implication of this Nab2 upregulation in D2-SPNs we knocked down Nab2 in NAc D2-SPNs and demonstrate reduced cocaine seeking after 10 days of cocaine self-administration. Using snRNA-seq, we identify distinct transcriptional signatures in D2-SPNs and dopamine receptor 1 expressing (D1)-SPNs after cocaine self-administration and these signatures are reversed with Nab2 knockdown in D2-SPNs while also altering D1-SPN transcriptomes. Collectively, our studies demonstrate that blocking a transcriptional corepressor in D2-SPNs blunts cocaine seeking, while also shifting the transcriptional landscape in these neuron subtypes and other NAc projection neuron subtypes.