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Phosphodiesterase 1b is an Upstream Regulator of a Key Gene Network in the Nucleus Accumbens Driving Addiction-Like Behaviors

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Cocaine use disorder (CUD) is a serious public health issue with no effective pharmacotherapies. Identifying treatments for CUD is hindered in part by an incomplete understanding of the coordinated changes in gene expression that drive maladaptive plasticity and addiction-like behaviors. In this study, we conducted unbiased gene network analysis on a published RNA sequencing (RNA-seq) dataset from 6 different brain regions of animals that underwent cocaine self-administration followed by prolonged withdrawal plus context- or cocaine-induced reinstatement (Walker et al., *Biol Psychiatry*, 2018). We ranked gene networks by their fold enrichment in genes whose expression is significantly correlated with the "Addiction Index" (AI) – a composite score developed by machine learning to capture maladaptive, addiction-like behaviors during cocaine self-administration. We identify the gene encoding phosphodiesterase 1b (*Pde1b*), a Ca^{2+}/calmodulin-dependent enzyme that catalyzes the hydrolysis of cAMP and cGMP, as the strongest regulator of a gene network in the nucleus accumbens (NAc) that shows the highest magnitude association with the AI of all gene modules in this brain region. To investigate the role of *Pde1b* in regulating addiction-like behaviors, we will deliver *Pde1b*-targeting clustered regularly interspaced short palindromic repeats (CRISPR) activation and interference (CRISPRa/i) tools into the NAc and perform conditioned place preference (CPP) and self-administration for cocaine. Additionally, we will use RNA-seq to measure the effect of *Pde1b* manipulation on gene network activity and cocaine-induced transcriptomic changes in the NAc. Given successful drug discovery efforts focused on other PDE isoforms, this work may present a novel therapeutic approach for CUD.