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Circuit-wide gene network analysis reveals a role for phosphodiesterase enzymes in cocaine addiction

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Cocaine use disorder (CUD) is a serious public health issue without an effective pharmacological treatment. Novel treatments for CUD are hindered in part by an incomplete understanding of the molecular mechanisms in the brain that drive long-lasting maladaptive plasticity and addiction-like behaviors. In this study, we conducted unbiased gene co-expression network analysis on a published RNA sequencing dataset comprising 6 interconnected regions of the brain's reward circuity from mice that underwent saline or cocaine self-administration, followed by a 24-hour or 30-day withdrawal period and a saline or cocaine challenge. We ranked gene networks by their fold enrichment in genes whose expression is significantly correlated with an "addiction index" (AI) – a composite score developed using factor analysis to capture maladaptive, addiction-like behaviors during cocaine self-administration. We identify phosphodiesterase 1b (*Pde1b*), a Ca^{2+}/calmodulin-dependent enzyme that catalyzes the hydrolysis of cAMP and cGMP, as a key driver of a gene network in the nucleus accumbens (NAc) that exhibits a strong negative correlation with the AI. Cell-type-specific measurements of *Pde1b* expression reveal dynamic regulation of *Pde1b* within *Drd1*- and *Drd2*-expressing medium spiny neurons (D1 and D2 MSNs) over the course of cocaine administration. Viral-mediated overexpression of *Pde1b* in D1 or D2 MSNs oppositely regulates the behavioral response to cocaine, including cocaine-induced locomotor activity and cocaine self-administration. Our ongoing studies are investigating the role of *Pde1b* in regulating cocaine-induced transcriptomic changes within the NAc. Given successful drug discovery efforts focused on other PDE isoforms, this work may guide novel therapeutic development for CUD.