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Transcriptional reprogramming of the brain reward system by heroin self-administration

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Opioid abuse exacts a devastating toll on individuals, their families, and the healthcare system. Treating opioid addiction is exceptionally difficult because even after prolonged abstinence re-exposure to the drug or to drug-associated cues can trigger relapse to compulsive drug-seeking. This is mediated in part by persistent changes to gene expression programs within interconnected reward-processing regions of the brain. Few studies have performed transcriptome-wide analyses throughout the reward system following volitional opioid intake. Here, we combine heroin self-administration in mice, next-generation RNA sequencing (RNA-seq), and bioinformatic analyses to identify novel genes and gene networks throughout the reward system that are regulated by opioid abuse. First, mice underwent 15 daily 4h sessions of intravenous heroin self-administration (0.05 mg/kg/infusion; FR1 schedule). Mice were then euthanized either 24h after the last self-administration session or following a 30-day withdrawal period. In the 30-day condition, mice received either a saline or heroin injection (1 mg/kg) and were placed back into self-administration chambers to measure drug-primed and/or context-induced reinstatement of heroin-seeking under extinction conditions for 2h, after which mice were immediately euthanized. Six brain regions involved in various aspects of reward-processing were collected and processed for RNA-seq: prefrontal cortex, nucleus accumbens, dorsal striatum, basolateral amygdala, ventral hippocampus, and ventral tegmental area. We are currently analyzing this RNA-seq dataset to identify key drivers of transcriptional regulation in opioid abuse, and contrasting the results with similar datasets generated with cocaine in our lab (Walker et al., 2018, Biol Psych) to delineate shared and distinct molecular signatures of addiction.