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Transcriptome profiling of the brain's reward circuitry in heroin self-administration identifies a ventral hippocampus gene network related to relapse susceptibility

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Opioid abuse exacts a devastating toll on individuals, their families, and the healthcare system. Treatment of opioid abuse is made exceptionally difficult by a prolonged susceptibility to relapse into compulsive drug-seeking and taking, often triggered by re-exposure to drug-associated cues or the drug itself. Long-term susceptibility to relapse may be supported by persistent changes to gene expression programs within interconnected brain regions critical for reward processing. To identify novel genes and gene networks driving opioid abuse, we combined heroin self-administration in mice, RNA sequencing (RNA-seq) throughout the reward system, and advanced bioinformatic analyses. Mice underwent a 15-day intravenous heroin self-administration paradigm and were then separated into two cohorts, euthanized either 24 hours after the last session or after a 30-day withdrawal period. In the 30-day condition, mice received either saline or heroin and were placed back into self-administration chambers to measure context-induced and drug-primed heroin-seeking for two hours. RNA-seq was conducted on six brain regions: medial prefrontal cortex, nucleus accumbens, dorsal striatum, basolateral amygdala, ventral hippocampus, and ventral tegmental area. Employing multiscale embedded gene co-expression network analysis (MEGENA), we identified a unique gene network in the ventral hippocampus specifically associated with heroin-seeking. Enriched with genes linked to chromatin remodeling, this network may mediate persistent changes in ventral hippocampal function underlying drug-seeking. Current work uses viral-mediated gene manipulation strategies targeting crucial hub genes in this network in addition to epigenome profiling of key histone tail modifications to gain mechanistic insight into the role of this gene network in relapse-liked behavior.