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Transcriptomics associated with opioid craving in the nucleus accumbens of male and females Long Evans rats

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Drug craving elicited by exposure to previously drug-paired cues is one of the most potent triggers of relapse. In substance use disorder patients as well as in animal models of addiction, a time dependent increase in cue-induced drug craving termed incubation of craving has been consistently reported. The goal of this research is to better understand the mechanisms driving this progressive intensification of cue-related drug craving. Long Evans male and female rats were trained to intravenously self-administer morphine for ten days, control animals received saline. After either one or thirty days of forced abstinence, tissue was collected from the nucleus accumbens shell, total RNA was extracted and assessed by RNA sequencing. Differential gene expression (DEG) analyses comparing saline- to morphine-treated rats after 30 days of abstinence revealed 190 DEGs for males and 744 for females. Gene ontology and pathway analyses of male gene sets suggest enrichment in genes involved in DNA regulation of transcription, alternative splicing, protein kinases, and phosphorylation of proteins. Female gene ontology and pathway analyses indicated perturbations in axon guidance, chemical synaptic transmission, calcium signaling and cholinergic synapses. Our results indicate that the time- dependent changes in gene expression associated with extended abstinence from chronic morphine self-administration diverge based on biological sex. In males, the nur nuclear orphan receptor subfamily of transcription factors may contribute to changes in gene expression in the accumbens. Ongoing studies are aimed at functionally validating the role of these transcription factors and their target genes on mediating incubation of craving in males.