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Relating individual differences in vulnerability to morphine self-administration in rats to gene expression in the medial prefrontal cortex (mPFC)

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Understanding mechanisms underlying individual differences in opioid addiction vulnerability is essential for developing more effective strategies for prevention and treatment. We are using RNA-seq to evaluate how gene regulation in the rat mPFC varies as a function of Withdrawal-Induced Anhedonia (WIA) after acute morphine administration. This vulnerability marker predicts the magnitude of various measures of subsequent morphine self-administration (MSA). We are also evaluating gene regulation as a function of the magnitude of behavioral economic Demand and Reinstatement, two such measures of MSA. Our initial experiments indicate that all three paradigms reveal a substantial number of functionally relevant genes where gene expression covaries with the magnitude of behavior. One emerging theme is the involvement of cholinergic-pathway genes in WIA. Specifically, the postsynaptic α5 cholinergic receptor subunit (CHRNA-5) and the presynaptic acetylcholinesterase membrane anchor precursor PRiMA (PRIMA1) were among the top-ranked genes whose activity varied as a function of WIA magnitude. In addition, TCF7L2, a transcription factor implicated in nicotine addiction, was the highest ranked upstream regulator implicated in WIA magnitude. Our preliminary data also indicate that expression of a substantial number of genes covaries with both WIA and Demand or Reinstatement magnitude. For example, 62 of the 266 genes showing significant covariance between gene expression and magnitude of Demand also show significant covariance between gene expression and WIA intensity. This points towards common genetic machinery underlying individual differences in acute morphine withdrawal and long-term MSA. We are currently assessing chromatin accessibility via ATAC-seq to investigate epigenetic mechanisms underlying these effects.