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Common and unique patterns of gene expression and chromatin accessibility in the rat medial prefrontal cortex across different phases of opioid use disorder

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The goal of this study is to characterize molecular mechanisms underlying individual differences in vulnerability to opioid use disorder (OUD) to inform the development of more effective prevention and treatment strategies. We are investigating the transcriptome (RNA-seq) and genome-wide chromatin accessibility (ATAC-seq) in the medial prefrontal cortex (mPFC) of male and female rats given morphine and exhibiting differential vulnerability to OUD as measured in behavioral paradigms capturing different phases of the disorder: Withdrawal-Induced Anhedonia (WIA), Demand, and Reinstatement. Ingenuity Pathway Analysis (IPA) of RNA-seq revealed greater changes in canonical pathways in Resilient (vs. Saline) rats in comparison to Vulnerable (vs. Saline) rats across 3 paradigms, suggesting brain adaptations that might contribute to resilience to OUD. Weighted Gene Co-Expression Network Analysis (WGCNA) showed decreased connectivity of a myelination/oligodendrocyte gene network module in morphine-WIA rats and in an inflammation module in morphine-Demand rats. Follow-up IPA analyses indicated altered activity in canonical pathways and upstream regulators consistent with these functions. HOMER motif analysis of ATAC-seq showed changes in accessibility to a small set of transcription factor (TF) binding sites, some that were shared across the 3 paradigms and others that were unique to each. In conclusion, we have identified changes in biological pathways, TFs, and their binding motifs that vary with paradigm and disease vulnerability. These findings point to the involvement of distinct transcriptional and epigenetic mechanisms in response to opioid exposure, vulnerability to OUD, and different stages of the disorder.