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Epigenetic Regulation in the Medial Prefrontal Cortex Underlying Vulnerability to Opioid Use Disorder Throughout its Trajectory in Male and Female Rats

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Opioid use disorder (OUD) is associated with altered patterns of gene expression and their regulation. Little is known, however, about how these changes occur along the trajectory from initial drug exposure to OUD. We investigated genome-wide transcription (RNA-seq) and chromatin accessibility (ATAC-seq) in the medial prefrontal cortex of male and female rats in three paradigms modeling the initial response to passive, repeated morphine exposure (Withdrawal-Induced Anhedonia (WIA)), persistent use (Demand), and relapse (Reinstatement). Weighted Gene Co-Expression Network Analysis revealed decreased connectivity in a myelination/oligodendrocyte gene network module in morphine-exposed WIA rats and in an inflammation module in morphine-self-administering Demand rats. Follow-up Ingenuity Pathway Analysis indicated sex-specific alterations in activity in canonical pathways and upstream regulators consistent with these functions. We next conducted a Variance Partitioning Analysis to identify transcriptional signatures associated with OUD resilience or vulnerability across all three paradigms. We found that variation in gene expression attributable to OUD vulnerability was associated with epigenetic regulation across the three paradigms. HOMER motif analysis of ATAC-seq data revealed changes in accessibility to a small set of transcription factor (TF) binding sites, some that were shared by the 3 paradigms and others that were unique to each. In conclusion, we have identified changes in gene networks, upstream regulators, biological pathways, and TF binding motifs that are either phase-specific or span all three phases along the OUD trajectory. We have also identified a set of changes that covary with individual differences in OUD vulnerability.