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Sex-specific Concordance of Striatal Transcriptional Signatures of Opioid Addiction in Human and Rodent Brains

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Opioid use disorder (OUD) has emerged as a severe, ongoing public health emergency. Current, frontline addiction treatment strategies fail to produce lasting abstinence in most users. This underscores the lasting effects of chronic opioid exposure and emphasizes the need to understand the molecular mechanisms of drug seeking and taking, but also how those alterations persist through acute and protracted withdrawal. Here, we used RNA sequencing in post-mortem human tissue from males (n=10) and females (n=10) with OUD and age and sex-matched comparison subjects. We compared molecular alterations in the nucleus accumbens (NAc) and dorsolateral prefrontal cortex (DLPFC) between humans with OUD and rodent models across distinct stages of opioid use and withdrawal (acute and prolonged) using differential gene expression and network-based approaches. We found that the molecular signature in the NAc of females with OUD mirrored effects seen in the NAc of female mice at all stages of exposure. Conversely, males with OUD showed strong overlap in expression profile with rats in acute withdrawal. Co-expression networks involved in post-transcriptional modification of RNA and epigenetic modification of chromatin state. This study provides fundamental insight into the converging molecular pathways altered by opioids across species. Further, this work helps to disentangle which alterations observed in humans with OUD are driven by acute drug exposure and which alterations are consequences of chronic exposure.