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Morphine Self-Administration and Withdrawal Produce Sex- and Cell Type-Specific Transcriptomic Changes in the Rat Nucleus Accumbens

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The nucleus accumbens (NAc) is a central region in the reward pathway and relevant to the neurobiology of drugs of abuse, including opioids. We previously published single nucleus RNA sequencing (snRNAseq) results demonstrating that acute injection or 10-day self-administration of morphine causes transcriptomic changes in specific cell populations within the NAc of male rats. Here, we use snRNAseq to extend these findings to female rats to study sex differences, as well as assessing the transcriptomic effects of opioid withdrawal. A cohort of Sprague Dawley rats (n=48; 24 males, 24 females) were randomly assigned to three timepoints: 1) acute morphine injection or saline control; 2) 10-day intravenous morphine self-administration with sex-matched, yoked saline control; and 3) 10-day self-administration with yoked saline control followed by 10 days of forced abstinence. 10x Genomics snRNAseq libraries were generated from nuclei isolated from NAc punches. Count data were analyzed with the R package Seurat, resulting in identification of all expected glial and neuronal populations. Cell type-specific differentially expressed genes (DEGs) were observed at all morphine timepoints compared to the saline controls in both glia and neuronal subtypes. DEGs differed between the sexes and timepoints, supporting previous observed differences between acute morphine and 10-day self-administration, and identifying novel cell type-specific effects during opioid withdrawal. Bioinformatic analyses identified upstream regulatory mechanisms and downstream signaling pathways associated with these cell type-specific DEGs. These snRNAseq findings further our understanding of the neurobiology of opioid exposure and abstinence, and highlight potential cellular targets for the treatment of withdrawal.