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Transcriptomic characterization of the nucleus accumbens in an animal model of opioid use disorder using single-nuclei RNA sequencing

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Prior studies investigating the effects of opioids on the neural transcriptome primarily examined bulk tissue, limiting our understanding of the roles played by specific cell types. While a recent study characterized the cell type-specific effects of acute morphine exposure in the mouse nucleus accumbens (NAc), the effects of voluntary morphine taking and seeking are unknown. We sought to validate and extend this study by using a high-throughput single nuclei RNAseq approach to examine cell type-specific NAc transcriptomes after a single acute injection of morphine or 10-days of morphine self-administration in male Brown Norway rats. We sequenced ~190,000 nuclei and identified 27 transcriptomically distinct NAc cell types. Analysis of differential gene expression identified ~1,100 and ~2,400 differential expressed genes (DEGs) in the acute exposure and self-administration phenotypes, respectively. Intriguingly, DEGs for both phenotypes were concentrated in the same neuronal, astrocytic, and oligodendrocytic cell subtypes. Furthermore, while a portion of the cell type-specific DEGs associated with acute morphine and morphine self-administration overlap, a substantial portion was unique to either phenotype, raising the possibility that variance in the DEGs identified may be related to volitional opioid-taking. Downstream analyses identified enrichment of DEGs for cell type-specific GO terms, canonical pathways, and predicted upstream regulators that are consistent with literature evidence. This study furthers our understanding of the molecular mechanisms underlying acute and chronic exposure to opioids and demonstrates the benefits of preclinical neural single nuclei transcriptomics in studies of substances use disorders.