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Single nuclei transcriptomic analysis of rat nucleus accumbens reveals cell type-specific patterns of gene expression associated with volitional morphine

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Opioid exposure causes transcriptomic changes in the nucleus accumbens (NAc). However, no studies have investigated cell type-specific transcriptomic changes associated with volitional opioid taking. We used single nucleus RNA sequencing (snRNAseq) to comprehensively characterize transcriptomes of 190,030 NAc nuclei in rats self-administering morphine. One cohort of rats was injected with acute morphine (10mg/kg, i.p.) or saline. A second cohort self-administered intravenous morphine (1mg/kg/infusion) for 10 consecutive days. Each morphine-experienced rat was paired with a yoked saline control rat. snRNAseq libraries were generated from NAc punches and used to identify differentially expressed genes (DEGs) associated with volitional morphine taking. We identified 1106 DEGs in the acute morphine group, compared to 2453 DEGs in the morphine self-administration group, across 27 distinct cell clusters. Importantly, we identified 1329 DEGs that were specific to morphine self-administration. DEGs were identified in novel clusters of astrocytes, oligodendrocytes, and D1R- and D2R-expressing medium spiny neurons in the NAc. Cell type-specific DEGs included Oprm1, Pde10a, Rgs9, and Celf5, the latter two of which were validated by smFISH. Approximately 85% of all oligodendrocyte DEGs, nearly all of which were associated with morphine taking, were identified in two subtypes. Bioinformatic analyses identified cell type-specific upstream regulatory mechanisms of the transcriptome alterations and downstream signaling pathways, including novel and previously identified molecular pathways. These findings show that volitional morphine taking is associated with distinct cell type-specific transcriptomic changes in the rat NAc and highlight specific striatal cell populations and novel molecular substrates targetable to reduce compulsive opioid taking.