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Single-cell transcriptomics reveals that reduced glucose metabolism is linked to addiction-like behavior in rats

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The United States faces an epidemic of substance use disorders with an alarming increase in overdose deaths involving stimulants, such as cocaine. However, we still have limited knowledge of the cell type-specific mechanisms underlying cocaine addiction.

Prior studies examining the effects of cocaine exposure on gene expression changes in the rodent brains primarily analyzed bulk tissues, hindering our understanding of how distinct cell types respond to cocaine. While a recent single-cell transcriptomic study examined the effect of acute cocaine administration on individual cells of the rat nucleus accumbens (NAc), the impact of voluntary drug-taking and prolonged abstinence in rats is unknown.

Here we applied single-nuclei (sn)RNA-seq to the amygdala of heterogeneous stock (HS) rats trained to self-administer cocaine under extended access conditions and subjected to 5 weeks of abstinence. We compared HS rats classified as having a low or high addiction index based on several behavioral measures of addiction severity. We identified cell-type-specific genes that were differentially expressed between rats with low and high addiction indexes. Pathway enrichment analysis revealed that several signaling pathways were perturbed by cocaine use in a cell type-specific manner, including changes in glucose metabolism. By perturbing a step of the glycolysis pathway, we rescued key cellular and behavioral measures associated with addiction-related phenotypes.

Our work has unveiled a new cell-type-specific transcriptional mechanism associated with cocaine addiction that advances our understanding of the molecular basis of the neuroadaptations induced by long-term use of cocaine.