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Cell type-specific multi-omics analysis of cocaine use disorder in the human caudate nucleus suggests phosphodiesterases as a pharmacological target

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Structural and functional alterations have been reported in the reward circuitry of the human brain in cocaine use disorder (CUD) but their molecular underpinnings remain poorly understood. Epigenetics and gene expression are highly cell-type specific highlighting the need for studying the CUD brain at single-cell resolution.

We investigated human postmortem brain tissue (N=14) from the caudate nucleus using multi-omic RNA and ATAC profiling in 31,178 single nuclei. After the identification of 13 clearly delineated cell types, among them a variety of inhibitory neurons including D1- and D2-medium spiny neurons (MSNs), astrocytes, microglia, and oligodendrocytes, we investigated CUD-associated differential expression and altered chromatin accessibility.

Upregulated genes were related to phosphodiesterase and NADH-related metabolic processes, whereas downregulated genes suggested a neuron-specific downregulation of calcium channel and GABA-A receptor activity. A conserved set of upstream regulatory transcription factors was identified in RNA/ATAC imputed gene regulatory networks, including *ZEB1* and *TCF4,* suggesting a set of master regulators of altered gene expression profiles in CUD.

We performed the first study that investigated RNA-seq and ATAC-seq data from the same cell in CUD postmortem human brain tissue and found converging evidence for cell-type specific molecular alterations related to calcium and phosphodiesterase signaling. Phosphodiesterase inhibitors could constitute a novel treatment for CUD, as they have been shown to reduce cocaine self-administration and cue-induced reinstatement of cocaine seeking in rodent models. Our study thus emphasizes the value of cell type-specific approaches in translational addiction research and provides new insights into the neurobiology of CUD.