Name: Samar Nasser Chehimi, Ph.D. Email: samar.chehimi@pennmedicine.upenn.edu

Cocaine self-administration induces cell-type–specific transcriptional changes in the nucleus accumbens of rats

Chronic consumption of neurostimulants, such as cocaine, can lead to addiction-related and anxiety-like behaviors and represents a major public health issue. Although cocaine is known to alter neuronal activity, dendritic architecture, and cause other neurobiological effects, the molecular mechanisms underlying these adaptations remain unclear. To define cell-type–specific transcriptional changes caused by cocaine self-administration, we performed single-nucleus RNA sequencing on the nucleus accumbens (NAc), a key brain region mediating reward and drug-seeking behaviors. A group of male and female rats that self-administered cocaine (0.245 mg/mL/infusion, I.V.; n=4/group) for 10 consecutive days were evaluated and compared to saline yoked controls. Following the final session, animals were sacrificed, brains were collected and snap-frozen in isopentane, and the NAc was punched and processed for nuclei isolation. Individual nuclei were barcoded using the 10x Genomics Chromium controller to enable single-nucleus transcriptomic profiling. Cocaine exposure induced robust cell-type-specific transcriptomic changes, with the greatest number of differentially expressed genes (DEGs) observed in medium spiny neurons (MSNs) and astrocytes. One D1 MSN cluster previously localized to the NAc core was found to be particularly vulnerable to cocaine self-administration. These findings provide valuable information about the molecular adaptations in the NAc and may inform the identification of novel therapeutic targets for substance use disorders.

Authors:

Submitter: Samar Nasser Chehimi, Research Specialist, University of Pennsylvania, Philadelphia
Richard Crist, Ph.D., University of Pennsylvania
Riley Merkel, BSc, University of Pennsylvania
Benjamin Reiner, Ph.D., University of Pennsylvania
Heath Schmidt, Ph.D., University of Pennsylvania
Jackson Shuey, BSc, University of Pennsylvania

DRAFT