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Comparative single-cell multi-omic atlases of molecular adaptations associated with substance use and HIV infections in the prefrontal cortex and nucleus accumbens of humans, non-human primates, and rodents

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Substance use disorders (SUD) and addiction are associated with the dysregulation of neural circuits related to salience and habits, negative emotional states, and executive function, but the critical cell types within these brain regions are not fully described, and the best therapeutic targets within them are not known. The SCORCH consortium has identified key regions of the brain to study the impact of opioids and HIV on reward circuitry across multiple species and with a variety of single cell transcriptomic and epigenetic approaches. Here we report on integrative analyses within the prefrontal cortex (PFC) and nucleus accumbens (NAc), two regions particularly impacted by HIV and repeated drug exposure. We have constructed cell type atlases for both the PFC and NAc that encompass multiple species and SUD/HIV conditions. Rodent and non-human primate samples provided a controlled drug exposure and single viral species paradigms which provided clear biological signatures that assisted in identifying effects in genetically diverse human samples. Our PFC atlas contains single-cell multi-omic profiles of 367,219 cells from the dorsolateral PFC of 54 human donors, and a separate rat PFC atlas encompasses 272,816 cells across 37 individuals, half of which were HIV+. The NAc atlas contains 482,443 cells from human, mouse and rat across 8 studies, including HIV and multiple drug types. Our analyses describe PFC and NAc cell type-specific gene expression and chromatin accessibility changes associated with SUD, HIV, and SUD+HIV. Comparisons between humans and animal models will enable us to identify gene networks associated with specific substances and stages of addiction, then evaluate the dynamics of these gene networks in human donors. These analyses provide insights into the mechanisms of SUD and HIV in the PFC and NAc and serve as a blueprint for collaborative studies of >15 brain regions.