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Single cell multi-omics of the rhesus macaque striatum reveal regulatory mechanisms underlying the genetic basis of addiction

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Medium spiny neurons (MSNs) within the dorsal and ventral striatum integrate neuronal signals driving reward. These circuits become co-opted during substance use leading towards addiction. We recently reported transcriptionally distinct MSN subtypes in the non-human primate (NHP) striatum.

To investigate the role of these MSN subtypes on the reward circuit and addiction, we jointly profiled the transcriptome (RNA) and epigenome (ATAC) of the rhesus macaque with single cell multi-omics. Within each MSN subtype, we identified domains of regulatory chromatin (DORCs), open chromatin that drive local gene transcription. We find clusters of DORCs hierarchically differentiating MSN subtypes that are organized by the neurochemical signaling (D1 vs. D2), compartment (striosome vs. matrix), and region (dorsal vs. ventral striatum) of each MSN subtype.

Next, we mapped to the DORCs to human genome, applied LD score regression to intersect the MSN DORCs with recently published genome-wide association studies (GWAS) on substance use and substance use disorder traits, and identified cell types with significant heritability enrichment for genetic risk of addiction traits. For well-powered addiction related GWAS, we colocalized human variants to the likely target gene with MSN subtype DORCs. Lastly, we trained machine learning models of MSN subtype-specific chromatin to predict the regulatory and cell type impacts of human variants associated with addiction traits. These findings of cell type-specific gene regulation in the NHP striatum provide primate-unique lens to inspect conserved gene-regulatory mechanisms underlying the reward neural circuits and genetic risk for addiction.