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Single-nucleus transcriptome analysis reveals cell type-specific molecular signatures across reward circuitry in the human brain

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Single-cell/nucleus technologies are powerful tools to study cell type-specific expression in the human brain, but most large-scale efforts have focused on characterizing cortical brain regions and their constituent cell types. However, additional brain regions - particularly those embedded in basal ganglia and limbic circuits - play important roles in neuropsychiatric disorders and addiction, suggesting a critical need to better understand their molecular characteristics. We therefore created a single-nucleus RNA-sequencing (snRNA-seq) resource across five human brain regions (hippocampus, HPC; dorsolateral prefrontal cortex, DLPFC; subgenual anterior cingulate cortex, sACC; nucleus accumbens, NAc; and amygdala, AMY), with emphasis on the NAc and AMY, given their involvement in reward signaling and emotional processing. We identified distinct and potentially novel neuronal subpopulations, which we validated by smFISH for various subclasses of NAc interneurons and medium spiny neurons (MSNs). We additionally benchmarked these datasets against published datasets for corresponding regions in rodent models to define cross-species convergence and divergence across analogous cell subclasses. We characterized the transcriptomic architecture of regionally-defined neuronal subpopulations, which revealed strong patterns of similarities in specific neuronal subclasses across the five profiled regions. Finally, we measured genetic associations between risk for psychiatric disease and substance use behaviors with each of the regionally-defined cell types. This analysis further supported NAc and AMY involvement in risk for psychiatric illness by implicating specific neuronal subpopulations, and highlighted potential involvement of an MSN population associated with stress signaling in genetic risk for substance use.