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Multi-Species Analysis of Non-Canonical Striatal Projection Neurons Reveals Distinct Profiles for Human Pain and Addiction Genetic Risk

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Striatal projection neurons (SPNs) are key players in addiction neurobiology, yet their diversity across species and links to human genetic risk for neuropsychiatric traits are not fully understood. To address this, we used a single-cell genomics approach across four mammalian species to examine the conserved heterogeneity of SPNs in molecular, spatial, synaptic, electrophysiological, and genetic contexts.

We generated a novel snRNA-seq dataset of the human postmortem nucleus accumbens (NAc) and integrated it with 14 other datasets from humans, primates, rats, and mice. Our analysis identified both canonical (D1 and D2) and unique SPN subtypes, including D1/2 Hybrid and D1-NUDAP populations, organized along dorsal-ventral and striosome-matrix gradients. Mouse MERFISH spatial transcriptomics validated these findings.

Using this cross-species data, we linked SPN subtypes to human genetic risk for neuropsychiatric conditions, revealing enrichment patterns for addiction and pain-related genetic risks, particularly in the D1/2 Hybrid population. Molecular profiling highlighted unique synaptic specializations and predicted functional differences in synaptic proteins and neuronal activity.

This multi-omics approach provides new insights into SPN heterogeneity across species and its implications for understanding genetic risks associated with pain and addiction in humans. By integrating anatomical, transcriptomic, and genetic data, this study lays the groundwork for future research aimed at developing targeted treatments for addiction and pain.