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 heterogeneity across mammalian species and contributions to human genetic predisposition for pain and addiction remain incompletely understood. We employed a multi-mammalian, integrative approach to characterize SPN subtypes and link them to human genetic predisposition. Our study began with generating snRNA-seq of the ventral striatum from postmortem huam donors (N=2 females, N=2 males). We annotated and integrated these data with single cell RNA-seq and single cell ATAC-seq of human, monkey, rat, and mouse across 14 datasets. The multi-mammalian single cell consensus confirmed presence of eccentric SPNs (eSPN) across mammals in addition to canonical D1 and D2 SPN populations. One subpopulation are the D1/D2 hybrid SPNs which co-express *DRD1* and *DRD2* transcripts along with other transcripts distinct to eSPNs. Within each molecularly defined population exist dorsal-ventral and striosome-matrix gradients. These inferences from single cell data map onto published MERFISH spatial transcriptomics from the adult mouse striatum.

We then integrated this data with single-nuclei multi-omics analyses to develop a. To extend these findings, we performed cross-species integration of SPN datasets from multiple mammalian species, including human, non-human primate, and rodent data. This multi-mammalian analysis uncovered conserved SPN subtypes across species and allowed us to map these subtypes onto complementary spatial transcriptomics data, bridging anatomical and transcriptomic perspectives. Notably, we found that D1/D2 receptor co-expressing SPNs further differentiate into distinct subtypes based on spatial organization and conserved marker genes across species. By leveraging this cross-species integration, we were able to link each conserved SPN subtype to human genetic predisposition for neuropsychiatric conditions, with a particular focus on pain and addiction. Our results provide novel insights into striatal neuron heterogeneity

across mammals and its implications for understanding the genetic basis of pain and addiction susceptibility in humans, offering a foundation for future targeted investigations in addiction neurobiology and pain research.