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Multi-omic approaches for molecular mapping of reward circuitry in the human brain

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Mapping gene expression at cellular resolution within the anatomical context of human brain architecture improves our understanding of topographically organized brain regions and how they contribute to neuropsychiatric disorders, including substance use disorders. To define the molecular architecture of key anatomical hubs within brain reward circuitry, we used the 10x Genomics Visium and 3' single cell gene expression platforms to generate an integrated data-driven map of gene expression in the nucleus accumbens (NAc) of the adult human brain (n=10 neurotypical donors). We identified molecularly defined spatial domains, including regions enriched in *OPRM1*, and identified unique patterns of gene co-expression using non-negative matrix factorization. We also performed snRNA-seq and multiplex single molecule fluorescent in situ hybridization (smFISH) in the human habenula (Hb). We identified 10 distinct lateral and medial Hb cell types, many of which were spatially localized and showed conservation with cell populations identified in the rodent brain. Finally, we present preliminary data from novel methodological approaches to map individual gene transcripts at cellular resolution in the human brain, including Xenium *in situ* sequencing (10x Genomics) and long read sequencing coupled with Visium spatial transcriptomics in the dorsolateral prefrontal cortex (DLPFC). We share open-source, user-friendly analytical tools and web resources created for the scientific community to explore these rich single cell and spatial transcriptomics datasets. By integrating these datasets with neuropsychiatric and substance use disorder gene sets, we provide novel insights into how genetic risk for psychiatric disorders maps to underlying brain structure and function.