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Multiomic Profiling Reveals Cell Type-Specific Chromatin Accessibility in the Rat Nucleus Accumbens

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Enhancers transduce neuronal activity to cell type-specific transcriptional responses, driving long-lasting cellular adaptations. The nucleus accumbens (NAc) is a key region in the mesolimbic dopamine pathway, involved in reward-related learning and motivated behaviors. While previous work has demonstrated unique transcriptional mechanisms underlying plasticity in the NAc, the enhancers mediating cell-specific responses remain largely uncharacterized. This work uses paired single-nucleus RNA (snRNA-seq) and ATAC (snATAC-seq) to comprehensively profile the transcriptome and chromatin accessibility of ~68,000 NAc cells from 23 male and female rats. We identified 18 transcriptionally defined cell populations, including medium spiny neurons (MSNs), interneurons, and glial cell types. We identified >250,000 accessible chromatin regions across all cell types, predominantly in non-coding genomic regions. Using pseudo-bulk differential accessibility analysis with edgeR, we find that over 30% of significantly enriched regions (log2FC > 0, FDR < 0.05) exhibited cell type specificity. Activity-dependent transcription factor (TF) binding motifs, including AP-1 family members, are enriched across different MSN type-specific regions. By further characterizing these unique regulatory interactions and their effects on gene transcription, we aim to identify putative enhancer-mediated gene regulatory mechanisms. This work provides a hypothesis-generating foundation for characterizing and exploring unique cell types within the neuronal circuitry that regulates motivated behavior.