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Multiomic Analysis Uncovers Gene Expression and Chromatin Accessibility Changes in the Nucleus Accumbens of Rats After Cocaine Self-Administration

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Chronic exposure to cocaine and other psychostimulants is known to induce significant behavioral alterations, including anxiety-like behaviors and changes in locomotor activity. Cocaine taking also produces notable neurobiological effects, such as altered neuronal activity and modifications of dendritic density and morphology in medium spiny neurons within the nucleus accumbens (NAc), a critical brain region associated with reward. However, the molecular mechanisms underlying chronic cocaine taking within the NAc remain under investigation. This study identifies gene expression patterns and chromatin accessibility changes in the NAc of male and female rats allowed to self-administer cocaine for 10 consecutive days (0.245 mg/mL/infusion, I.V.; n=4/group), compared to saline yoked controls. Two hours following the final dose, animals were sacrificed, brains were flash-frozen, and the NAc was punched. Nuclei from the NAc were isolated, and through 10X Genomics Multiome assay, we evaluated chromatin accessibility and gene expression in the same nuclei. Our findings reveal cell type-specific transcriptome alterations and differentially accessible chromosomal regions induced by cocaine self-administration, with significant distinctions between sexes. We also observed changes in activation of canonical pathways, through Ingenuity Pathway Analysis, and disruptions in gene regulatory networks. These alterations highlight cell-type specific NAc multiomic signatures that are affected by cocaine taking, providing novel molecular targets for future interventions.