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Multiomic Signatures of Early Life Adversity Elucidate Mechanisms of Adult Addiction Trajectories

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Early life adversity (ELA) can have a lasting impact on mental health and the risk of developing substance use disorders (SUDs). However, the enduring neuromolecular mechanisms that underly increased adult SUD trajectories are poorly understood. The nucleus accumbens (NAc) is critically involved in acquisition and maintenance of SUDs and our prior work has identified NAc cell type-specific molecular mechanisms associated with the volitional drug taking. Here, we use combined single nuclei transcriptomics and epigenetics of the nucleus accumbens from adult male and female rats that were exposed to ELA, to identify the enduring cell type-specific multiomic signatures associated with adult alterations in drug taking behaviors. Male and female rats used in this study were reared in a normal housing environment with appropriate resources and enrichment or in a limited bedding and nesting (LBN) model, to delineate the effect of ELA. In LBN, pups are raised in a low-resource environment from postnatal days 2-9, after which all animals are returned to a normal housing environment. Adult ELA and normally housed animals were euthanized, brains flash frozen, and the NAc microdissected. Preparations of NAc nuclei were used for the 10x Genomics Multiome combined single nuclei RNAseq and ATACseq assay per manufacturer protocols. Downstream analyses identify sex- and cell type-specific alterations in gene expression, chromatin accessibility, canonical signaling, upstream regulation, and gene regulatory networks associated with ELA. These multiomic signatures further our understand of the lasting impact of ELA on SUDs and highlight cellular populations and mechanisms for future study.