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Cell Type-specific Changes in the Caudate Nucleus of Human Postmortem Brains Induced by Alcohol Use Disorder

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Alcohol use disorder (AUD) is a complex disease that affects millions of people worldwide. The caudate nucleus is a key brain region involved in reward processing and addiction. The goal of this research is to identify cell-type-specific gene expression and chromatin accessibility differences in the caudate associated with AUD and infer gene regulatory mechanisms underlying these differences.

We conducted a high-throughput single-nucleus RNA-seq assay and a single-nucleus multiome assay (RNA and ATAC-seq) on caudate tissue from human postmortem brain samples from 74 individuals with AUD and 69 without, in total measuring 1,121,762 cells. We identified 17 distinct cell types, including two subtypes of astrocytes and four of microglia, representing different biological states of activation. We found an increased proportion of microglia in an activated, inflammatory state in AUD, and more astrocytes in a reactive state. Through inference of cell-cell communication changes, we discovered that signaling from microglia to astrocytes via the pro-inflammatory cytokine interleukin-1 beta is increased in AUD.

We detected 4,577 genes differentially expressed in astrocytes and 8,412 in oligodendrocytes, which were enriched for genes involved in immune response and synaptic regulation, respectively. Differences in chromatin accessibility were correlated with these differences in gene expression, implying that regulation of chromatin accessibility may directly contribute to differential gene expression in AUD. Regulatory network analyses revealed that the observed transcriptional changes in astrocytes and oligodendrocytes were likely regulated by several bZIP family transcription factors. These results have enriched our knowledge of the molecular basis of AUD at the single cell level.