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## **Cell type-specific multiomic analysis of substance use disorders in outbred rats**

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It is hypothesized that addiction results from widespread transcriptional changes in the brain caused by chronic drug use. Interestingly, only some substance users transition to the addiction state and addiction is highly heritable, indicating that genetic variation mediates individual differences vulnerability to addiction. However, the mechanisms by which genetics drive addiction are not well understood. The majority of genetic risk variants for addiction are found in noncoding genomic regions, making it difficult to determine their functional effects. Furthermore, most studies of substance use disorders have been conducted on heterogeneous bulk tissue which cannot detect cell type-specific signals. This has impeded a comprehensive characterization of the mechanisms by which chronic drug use leads to neuroadaptations in the brain's reward system. We hypothesize that studying single cell sequencing data will yield a higher resolution understanding of the molecular basis of substance use disorders.

We have analyzed single-nuclei RNA-seq and ATAC-seq from the amygdala of outbred rats trained to self-administer cocaine and selected as vulnerable or resistant to compulsive cocaine use. Our analysis has revealed cell type-specific differentially expressed genes and differentially accessible open chromatin regions associated with vulnerability to cocaine addiction. We have also quantified allele specific expression and allele specific open chromatin in each cell type which will boost power for mapping expression and chromatin accessibility QTLs by jointly modeling allelic imbalance and read depth. Our discovery of cell type-specific regulatory mechanisms associated with addiction-related behaviors will advance understanding of the molecular basis of the neuroadaptations induced by long-term use of addictive drugs.