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Increased Somatic Mutation Rate and Transcriptome Noise in OUD Patients in Nac and Sgacc

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Opioid Use Disorder (OUD) is associated with various comorbidities, including sleep disturbances, mood disorders, respiratory dysregulation, and causes numerous social challenges. Significant efforts have been made to understand the molecular mechanisms underlying the development of OUD and its associated comorbidities. In our study, we observed an increased somatic mutation rate in specific cell types in subgenual anterior cingulate cortex (sgACC) and nucleus accumbens (NAc) of OUD patients using single-nuclei RNA and ATAC sequencing (multi-omic) data. We further validated some of these mutations through single-cell genome sequencing of identical brain regions from the same patients. Additionally, we characterized the distribution of somatic mutations at the single-cell level to explore the "clonal architecture" of somatic mutations that may be functionally related to OUD. Using the same multi-omic dataset, we also found that transcriptional noise (TN) was elevated in several sgACC cell types in OUD subjects. Given that increased TN has been observed in multiple organs during aging, this suggests that certain brain cells in OUD may undergo aging-like processes. We are integrating data on somatic mutations, differential gene expression, differential chromatin accessibility, and transcriptional noise to understand how OUD may contribute to brain dysfunction by disrupting transcriptional regulatory networks (TRN).