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Sequencing newly initiated transcripts to study transcriptional regulatory mechanisms in substance use disorders

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Altered gene expression patterns and dysregulated activity of various transcription factors (TFs) have been linked to long-lasting changes in neural circuits associated with substances use disorders. However, these regulatory mechanisms are not well established. Here, we begin to quantitatively dissect the components of transcriptional regulatory networks associated with substance use disorders. To this aim, we use a novel method, capped small (cs)RNAseq, that we developed to quantify newly initiated transcripts with high sensitivity and high spatial resolution directly from total RNA. csRNAseq can accurately define Transcriptional Start Sites (TSSs) of both stable and unstable transcripts, allowing the unbiased annotation of activated genes and transcribed regulatory elements (i.e. eRNAs), at single-nucleotide resolution. Compared to other epigenomic assays, csRNAseq identifies changes in activity at regulatory elements with higher dynamic range and better correlation with neighboring gene transcription changes. Thus, we used csRNAseq, in combination with ATAC-seq, to investigate the transcriptional regulatory mechanisms associated with behavioral changes observed during protracted abstinence from self-administered oxycodone under extended access conditions in Heterogenous stock (HS) rats. We identified several hundred TSSs that were differentially regulated in comparison with naïve rats, and we begun to identify their underlying transcription factor networks. Moreover, by comparing the regulatory landscapes of rat strains with low- versus high- susceptibility to OUD, we hope to facilitate the annotation of GWAS risk variants with regulatory functions. In summary, using this approach we will gain novel insights into the role of regulatory transcriptional activity in addiction.