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Transcriptional initiation profiling of primary brain cells to study stimulus-dependent enhancer activity

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Enhancer elements regulate cell type- and stimulus-specific gene expression and are enriched with genetic variants associated with human diseases. Studying regulatory mechanisms of enhancer activity is critical to elucidate how these variants contribute to disease, including those associated with substance use disorders (SUDs). I profiled nascent transcriptional start sites (TSSs) with capped small RNA-seq (csRNA-seq) to measure transcriptional activity of promoters and enhancers in mouse primary neurons and astrocytes in response to SUD relevant stimuli, including dopamine and forskolin in primary neurons and IL-1B in astrocytes. I annotated over 100,000 regulatory elements in each cell type, most of which initiate enhancer RNAs (eRNAs). Most genomic regions with one or more TSSs, which we called transcript start regions (TSRs) were cell type-specific, and analysis of these TSRs showed different TFs are implicated in establishing cell type-specific regulatory programs in each cell-type. Neuronal stimulation with forskolin activated enhancers enriched in motifs recognized by AP1 and CREB family TFs. Astrocyte stimulation with IL-1B activated enhancers enriched in motifs recognized by NFkB, AP1, and IRF family TFs. Analysis of motif distributions relative to the TSS revealed strong positional preferences for many of the TFs with regulatory elements. Intriguingly, the preferred positions for motifs recognized by CREB are different for TSS that are up- versus down-regulated in enhancers. This study has generated the first comprehensive catalog of eRNA TSSs in primary murine neurons and astrocytes and provides new insights into the mechanisms by which TFs regulate transcription in addiction-related pathways.