

Integrative analysis identifies long noncoding RNA dysregulation and circadian disruption in reward and executive circuits of opioid use disorder

Opioid use disorder (OUD) is characterized by compulsive drug seeking and impaired executive control arising from maladaptive plasticity within cortico–striatal circuits. While transcriptomic studies have identified coding gene alterations in the nucleus accumbens (NAc) and dorsolateral prefrontal cortex (DLPFC), the contribution of the noncoding genome remains poorly defined. Here, we performed integrative transcriptomic analysis of postmortem human NAc and DLPFC to systematically identify and characterize long noncoding RNAs (lncRNAs) in OUD. We identified 36,225 lncRNA loci expressed across reward and executive regions, approximately half of which were previously unannotated. OUD was associated with widespread lncRNA dysregulation in NAc and DLPFC, with lncRNA-centered co-expression modules enriched for neuroimmune signaling, phosphorylation-dependent synaptic pathways, and intracellular receptor cascades. Notably, OUD disrupted circadian rhythmicity of lncRNAs to a degree comparable to or exceeding mRNAs, implicating temporal reorganization of noncoding networks in addiction pathology. Integration with single-nucleus transcriptomic data revealed pronounced neuronal and glial cell type specificity among OUD-associated lncRNAs. Together, these findings demonstrate that lncRNAs represent a critical regulatory layer in reward and executive circuits and suggest that spatial, temporal, and cellular remodeling of the noncoding transcriptome contributes to circuit dysfunction in OUD.

Authors:

Submitter: Chan Zhou, Assistant Professor, UMass Chan Medical School, Worcester MA