

Name: Benjamin Reiner, Ph.D.

Email: bcreiner@pennmedicine.upenn.edu

Morphine isoforms and epitranscriptome signatures in accumbens subregions

Opioids remodel reward and stress circuitry, but region-specific isoforms, RNA modifications, and poly(A) dynamics remain incompletely defined. We generated a cohesive atlas of these transcriptome dynamics for chronic morphine responses in the nucleus accumbens core and shell using a native RNAseq long-read assay. Male rats (n=16) received twice-daily morphine for 14 days. We microdissected the nucleus accumbens shell and core, subregions separately. Poly(A)+ RNA was sequenced using ONT direct RNA sequencing (RNA004) on the PromethION platform. Reads were basecalled, aligned to the rat reference genome, and assigned to genes and isoforms for differential expression and isoform-switching analyses. Raw-signal features were additionally used to estimate poly(A) tail lengths and identify condition-associated epitranscriptomic signatures. Cross-region contrasts and pathway-level enrichment were used to contextualize signatures. Direct RNA sequencing produced long, full-length reads enabling concurrent detection of differential gene expression, isoform changes, non-canonical base modification signatures, and poly(A) tail length shifts. Morphine produced region-dependent responses, with both shared and divergent programs. PromethION native RNAseq provides an integrated view of transcriptional and post-transcriptional opioid adaptations perfect for atlas level sequencing across distributed brain circuits. Future efforts will expand to additional brain regions, time points, include females, and validate priority isoforms/modification sites with orthogonal assays and targeted long-read approaches.

Authors:

Submitter: Benjamin Reiner, Assistant Professor, University of Pennsylvania, Philadelphia
Samar Chehimi, Ph.D., University of Pennsylvania
Richard Crist, Ph.D., University of Pennsylvania
Heath Schmidt, Ph.D., University of Pennsylvania