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Transcriptional signatures in the human postmortem brain reveal associations between molecular rhythm disruptions and opioid use disorder

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Vulnerability to opioid relapse is associated with severe and persistent disruptions to sleep and circadian rhythms. The few studies in postmortem brains of subjects with OUD implicate corticostriatal circuit dysfunction, particularly within the dorsolateral prefrontal cortex (DLPFC) and nucleus accumbens (NAcc), and molecular mechanisms related to sleep. Improving sleep or circadian rhythms may be an effective intervention for mitigating cravings and reducing relapse. Therefore, uncovering links between brain rhythm disruptions and OUD will be critical for identifying novel therapeutics. In the current study, we collected DLPFC and NAcc from postmortem brains from subjects with OUD and controls (n=40). RNA-seq was performed on the tissue, followed by differential expression (DE) and pathway analyses, along with other exploratory approaches to reveal potential molecular mechanisms in OUD. We also employed molecular rhythm analyses using ‘time of death’. We discovered 402 DE genes in the NAcc and 326 DE genes in the DLPFC of OUD subjects. In OUD, pathway analyses revealed enrichment for oxidative stress, metabolism, immunity, and circadian rhythm signaling. Transcriptional alterations were strikingly similar between DLPFC and NAcc in OUD, suggesting opioid dependence is associated with coherence of molecular alterations in corticostriatal circuits. Hub gene network analyses revealed potential upstream regulators specific to OUD, including circadian and immune transcription factors. Preliminary circadian analyses also revealed a loss of molecular rhythms in the DLPFC and NAcc in OUD. Our findings begin to uncover the transcriptional alterations in the brain associated with OUD and further highlight the molecular links between rhythm alterations and opioids.