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Unraveling the interplay between neuroHIV and substance abuse with systems biology to shed light on novel druggable targets.

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Substance abuse in patients with HIV is associated with treatment non-compliance, greater risk of viral transmission, and more rapid clinical progression of HIV disease. Our interdisciplinary approach employs a systems biology framework in conjunction with gene expression profiling by RNA-Seq at the bulk and single nucleus levels in intravenous self-administration paradigms in HIV transgenic and wild type rats under conditions of either short access (ShA), which is characterized by a non-dependent, “recreational” pattern of drug use, or long access (LgA) conditions, which leads to escalated (dependent) drug intake. Parallel studies with stimulants and opioids self-administration are designed to highlight both common and diverse transcriptional dysregulations and candidate therapeutic targets. We employ network-based algorithms based on approaches that proved exceptionally effective in deconvolving molecular interactions in cancer. Our systems biology analyses are aimed at identifying key master regulator genes governing the gene signatures associated with escalated drug self-administration and HIV, their co-regulators and targets that can serve as candidate therapeutic targets to improve neuropsychological functioning in people with HIV and substance use disorder (SUD) comorbidity. We are currently leveraging the capabilities of the Scripps Molecular Screening Center to carry out high-throughput screenings to identify small molecule inducers of a candidate target for hypofrontality in SUD and neuroHIV inferred using the present experimental-computational strategy. The present strategy integrating transcriptomics, behavior methods, and computational strategies is an effective means to formulate novel testable mechanistic hypotheses that can lead to transformative new therapeutic concepts for SUD in the HIV setting.