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Enumeration and visualization of differential gene co-expression response to cocaine

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Patterns of cocaine use disorder and cocaine response behaviors vary across genetically diverse individuals. Genetic differences in cocaine-related behaviors across mouse strains can be used to detect biological mechanisms of variable addiction vulnerability. One important aspect of the transcriptional response to drug is the coupling and decoupling of gene expression patterns following drug exposure. We applied the widely-used Weighted Gene Co-expression Network Analysis (WGCNA) and Paraclique co-expression analysis with Permutation-based Maximum Covariance Analysis (PMCA) to identify differential co-expression networks in the striatum across thirty-four (34) cocaine-exposed and cocaine-naive Collaborative Cross strains. We evaluated these approaches by 1) considering the practical considerations of the algorithms, 2) assessing the concordance and divergence of the resulting networks to each other and importantly, to cocaine-relevant expertly curated gene sets in GeneWeaver, and 3) the strength of association of the co-expression networks with behaviors related to impulsivity and reversal learning, cocaine sensitization, and cocaine intravenous self-administration (IVSA). PMCA and Paraclique compared well while WGCNA scored lower when compared to cocaine-relevant gene sets. We designed innovative systems genetics visualizations that enable researchers to interact with and explore the correlation of cocaine-related behaviors, co-expression and differential co-expression networks to characterize behavioral, neurobiological and genomic associations to genes of interest. As more behavioral traits are characterized in the Collaborative Cross population, additional relations among genes and behavior can be found. Funded by NIH P50 DA039841 and R01 DA037927 to EJC.