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Genetic background-dependent variation in cocaine-modulated gene regulatory networks in the *Drosophila* brain

Drosophila melanogaster presents a powerful model system in which genetic background, environment and exposure conditions can be controlled precisely and differential gene expression can be analyzed in the entire brain in a single analysis. In previous studies we used single cell RNA sequencing in the standard laboratory *D. melanogaster* Canton-S (B) strain to show that acute exposure to cocaine causes widespread and sex-specific changes in genome-wide gene expression in the brain in both neuronal and glial cell populations. Recently, we measured cocaine consumption in 598 lines of the newly expanded *Drosophila* Genetic Reference Panel (DGRP3) and, using a two-choice feeding test, observed extensive genetic variation in cocaine consumption and preference. To identify gene regulatory networks that mediate genetic background-dependent and sex-dependent changes in gene expression upon cocaine consumption, we combined snATAC-seq and snRNA-seq for multi-ome analyses in brains from three DGRP3 lines with innate preference for cocaine consumption and three lines with cocaine preference indices at the population mean. We demonstrate genetic background-dependent, sex-specific and cell-type specific changes in chromatin accessibility and differential gene expression after acute exposure to cocaine and uncover complex gene regulatory networks associated with cocaine-mediated modulation of gene expression. Cocaine-induced chromatin accessibility changes and differential gene expression are genetic background-specific and sexually dimorphic across the six DGRP3 lines. Differences between the preference groups only become evident at the level of gene regulatory networks. Cocaine-sensitive gene regulation features prominently in specific neuronal and glial populations which are distinct between males and females but overlap in Kenyon cells of the mushroom bodies. Supported by NIH grant U01-DA041613 and P20-GM139769.

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