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The Drosophila Brain on Cocaine at Single Cell Resolution

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Whereas the neurological effects of cocaine have been well documented, effects of acute cocaine consumption on genome-wide gene expression across the brain remain largely unexplored. This question cannot be readily addressed in humans, but can be approached using the *Drosophila melanogaster* model, where gene expression in the entire brain can be surveyed at once. Flies exposed to cocaine show impaired locomotor activity, including climbing behavior and startle response (a measure of sensorimotor integration), and increased incidence of seizures and compulsive grooming. To identify specific cell populations that respond to acute cocaine exposure, we analyzed single cell transcriptional responses in duplicate samples of flies that consumed fixed amounts of sucrose or sucrose supplemented with cocaine, in both sexes. Unsupervised clustering of the transcriptional profiles of a total of 86,224 cells yielded 36 distinct clusters. Annotation of clusters based on gene markers revealed that all major cell types (neuronal and glial) as well as neurotransmitter types from most brain regions were represented. The brain transcriptional responses to cocaine showed profound sexual dimorphism and were considerably more pronounced in males than females. Differential expression analysis within individual clusters indicated cluster-specific responses to cocaine. Clusters corresponding to Kenyon cells of the mushroom bodies and glia showed especially large transcriptional responses following cocaine exposure. Cluster specific co-expression networks and global interaction networks revealed a diverse array of cellular processes affected by acute cocaine exposure. These results provide an atlas of sexually dimorphic cocaine-modulated gene expression in a model brain.