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Genetics and sex govern the striatum transcriptional response to cocaine

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Addiction vulnerability is highly heritable and addiction behaviors differ among the sexes. In the laboratory, addiction phenotypes depend on these organismal characteristics. Therefore, studies of addiction in non-human animals should account for these known biological sources of variation, yet addiction phenotypes in mice are often studied in a single sex and strain. Here, we test the dependency of the striatum transcriptome's response to cocaine on both genetic diversity and sex. Using RNA sequencing of striatum tissue from the eight founder strains of the Diversity Outbred and Collaborative Cross mouse populations, we assessed the main effects of repeated cocaine versus sham injection, genetic background, sex, and all interaction effects on global gene expression. Most effects were genetic – well over half of the genes expressed in the striatum were differentially expressed across founder strains – but no genes were differentially expressed through a main effect of cocaine. Instead, cocaine-related molecular phenotypes manifested as interactions with sex and genetic background, and the strongest cocaine exposure effects were attributable to cocaine's interaction with both sex and genetic background. A number of genes were upregulated after cocaine exposure in a sex and strain specific manner including the immediate early gene *Arc*, the dual specificity phosphatase gene *Dusp1*, and the conserved neuromodulatory miRNA gene *Mir212*. Altogether, these results demonstrate the context specificity of cocaine response mechanisms while reiterating the necessity of incorporating genetic diversity and sex differences when studying the biological basis of addiction. This mechanistic variation in response suggests potential mechanisms of differential vulnerability to addiction.