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Genetic variation and heritability of negative affective withdrawal from cocaine in the CC/DO founder mouse strains

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Negative mood states that characterize drug withdrawal are partly under genetic control and associated with craving and relapse to drug use in humans. We investigated negative mood states associated with cocaine withdrawal across the eight inbred Collaborative Cross (CC)/Diversity Outbred (DO) founder strains to determine their feasibility for future genetic mapping studies. We measured sucrose preference and immobility in the forced swim test (FST) following repeated saline or cocaine treatment to assess anhedonia and dysphoria. We identified a main effect of strain $F(7,184) = 4.79$, $p < 0.001$, partial eta squared = 0.15; and a main effect of drug $F(1,184) = 4.9$, $p = 0.029$, partial eta squared = 0.03 on sucrose preference. In addition, we identified a main effect of strain $F(7, 304) = 97.4$, $p < 0.001$, partial eta squared = 0.69; and a main effect of sex $F(1, 304) = 4.76$, $p = 0.03$, partial eta squared = 0.015, but not drug, on time spent immobile in the FST. Our results provide strong evidence for genetic differences associated with dysphoria and anhedonia in mice, and moderate evidence that cocaine withdrawal induces anhedonia. Future work will: 1) utilize a systems genetic approach to determine if negative affective withdrawal symptoms are correlated with other drug abuse phenotypes currently under investigation in the DO/CC, and 2) search for correlations between negative affective withdrawal symptoms and neuronal gene expression to identify gene co-expression networks that mediate the effects of withdrawal severity.