

## Measuring negative affective withdrawal in CFW mice: A pilot study

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Negative mood states that characterize drug withdrawal are partly under genetic control and have been associated with craving and relapse to drug use in humans. Mice can be used to model aspects of the negative mood states associated with amphetamine (AMP) withdrawal and offer a number of advantages relative to studies in humans. Here, we investigated negative mood states associated with AMP withdrawal using commercially available, outbred CFW mice to determine their feasibility for future QTL mapping studies. Mice were tested in the Elevated Zero Maze (EZM), Porsolt Forced Swim Test (FST), and Sucrose Preference Test to assess changes in anxiety-like behavior, dysphoria, and anhedonia following 14 consecutive days of 2.5 mg/kg AMP administration. A paired-samples t-test indicated withdrawal-induced enhancement of anxiety-like behavior as measured by increased time spent on the closed quadrants,  $t(276) = -2.66$ ,  $p < 0.008$ . We also observed a decrease in risk-assessment behaviors (i.e., head dips, stretch-attends) on the EZM during AMP withdrawal,  $t(276) = 15.5$ ,  $p < 0.001$ . In addition, there was a significant increase in FST immobility time during AMP withdrawal,  $t(326) = -15.97$ ,  $p < 0.001$ , as well as a decrease in latency to become immobile,  $t(325) = 6.60$ ,  $p < 0.001$ ; suggesting the mice exhibited dysphoric behavior due to withdrawal. Finally, we observed a significant decrease in sucrose preference during AMP withdrawal,  $t(218) = 2.42$ ,  $p < 0.16$ , indicating withdrawal-induced anhedonia. Importantly, we observed tremendous variation in all three traits which enables genetic mapping of naturally occurring genetic variation that is associated with trait variation. We predict that the phenotypic diversity displayed by this highly recombinant population will facilitate the discovery of genes and biological pathways underlying drug use disorders in humans.

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