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### **Measuring negative affective withdrawal in CFW mice: Implications for GWAS**

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Negative mood states that characterize drug withdrawal are partly under genetic control and have been associated with craving and relapse in humans. We investigated negative mood states associated with AMP withdrawal using outbred CFW mice to determine their feasibility for future GWAS mapping studies. Mice were tested for sucrose preference, in the Elevated Zero Maze (EZM), and using the Porsolt Forced Swim Test (FST) to assess changes in anhedonia, anxiety-like behavior, and dysphoria following repeated AMP administration. No changes in sucrose preference were observed during AMP withdrawal. However, a paired-samples t-test indicated withdrawal-induced enhancement of anxiety-like behavior as measured by decreased time spent on open quadrants of the EZM,  $t(656) = 4.2$ ,  $p < 0.001$ . Furthermore, we identified a sex-dependent effect of AMP withdrawal on anxiety-like behavior. Only male mice spent significantly less time in the closed quadrants of the elevated zero maze during AMP withdrawal,  $t(385) = 4.1$ ;  $p < 0.001$ . Finally, there was a significant increase in FST immobility time during AMP withdrawal,  $t(780) = -24.5$ ,  $p < 0.001$ , as well as a decrease in latency to become immobile,  $t(776) = 11.7$ ,  $p < 0.001$ ; suggesting the mice exhibited dysphoric behavior due to withdrawal. 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.