Cocaine withdrawal in the CC/DO founder mouse strains: Interstrain variation and heritability of negative affective withdrawal.

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Background

Negative mood states, including dysphoria and anhedonia, characterize cocaine withdrawal. These negative mood states commonly predicate craving and drug use relapse.

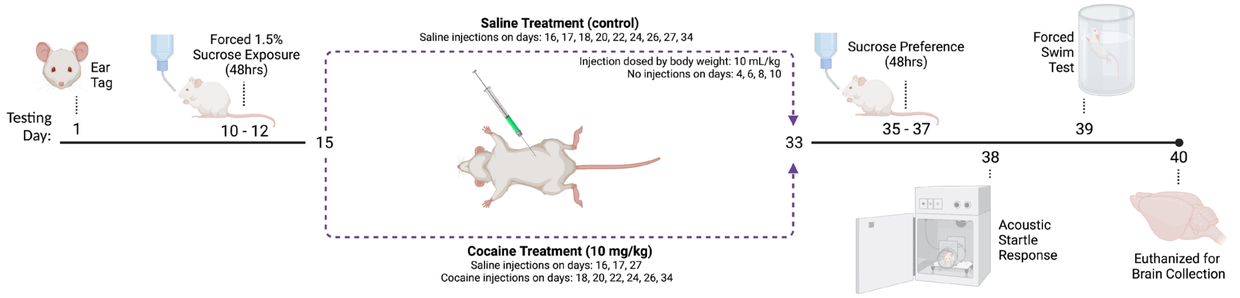
Negative mood states appear partially genetically mediated. Certain genetic factors may predispose individuals towards heightened withdrawal symptomatology and risk of relapse.

Studying panels of genetically diverse inbred mouse strains is a powerful approach to identify genes related to cocaine withdrawal. The Collaborative Cross (CC) and Diversity Outbred (DO) founder strains are eight distinct inbred strains with high allelic diversity, allowing more powerful and specific GWAS.

The CC/DO founder strains exhibit large behavioral variation that improves phenotypic assessment. Some of these strains may have extreme phenotypes that can be used as improved models of CUD. The DO mice could be utilized as a founder population for future genetic mapping of withdrawal-related genetic traits.

Methods

Eight CC/DO founder strains of both sexes were utilized. Mice were injected with either a saline or cocaine paradigm. Phenotyping during the withdrawal period included the Porsolt forced swim test (FST) and the sucrose preference test (with prior habituation). The sucrose preference test was modified during the experiment to a 48 hour time period. The mice were subsequently euthanized and their brains dissected.



Latency to Immobility in FST

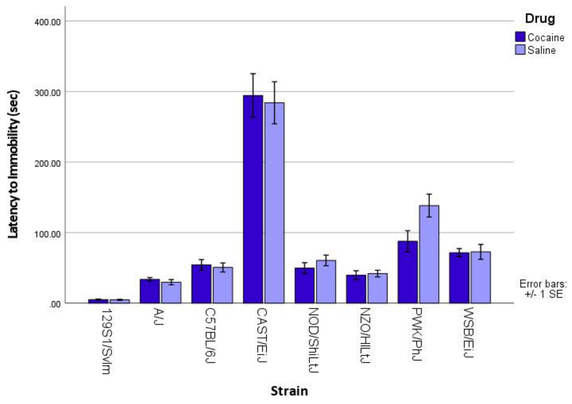


Figure 1. Mean latency to immobility during the FST for both sexes. There was a main effect of strain, $F(7, 248) = 96.262$, $p < 0.001$, $\eta_p^2 = 0.743$.

Time Spent Immobile in FST

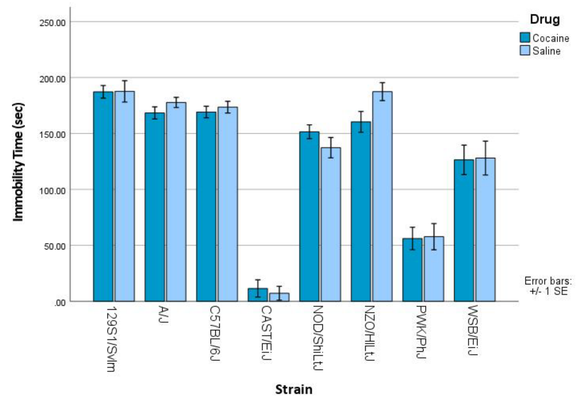


Figure 3. Mean immobility time during the FST for both sexes. There was a main effect of strain, $F(7, 248) = 96.262$, $p < 0.001$, $\eta_p^2 = 0.743$.

Sucrose Preference

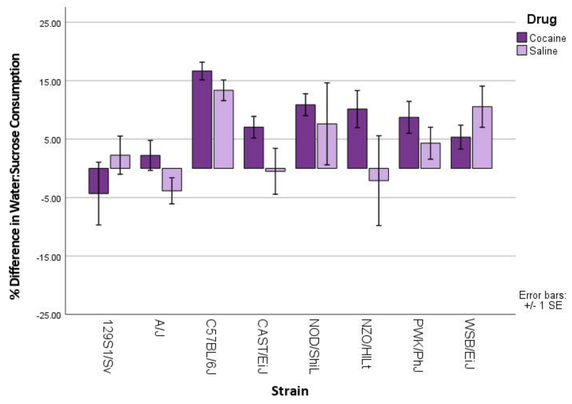


Figure 5. Mean sucrose preference, as measured in the % difference from null (50% consumption of both water and sucrose), for both sexes. There was a main effect of strain, $F(7, 130) = 4.262$, $p < 0.001$, $\eta_p^2 = 0.206$.

Female Mice

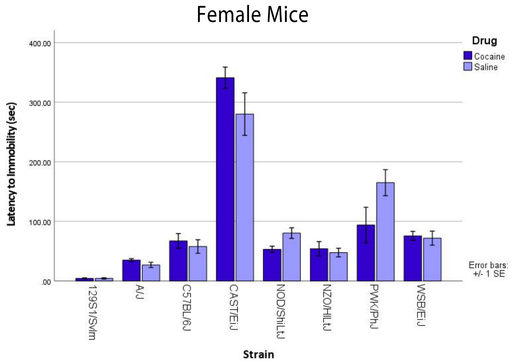


Figure 2. Mean latency to immobility during the FST for female mice. There was a significant interaction between strain and drug, $F(7, 115) = 2.745$, $p < 0.012$, $\eta_p^2 = 0.161$. There was a main effect of strain, $F(7, 115) = 70.814$, $p < 0.001$, $\eta_p^2 = 0.832$.

Female Mice

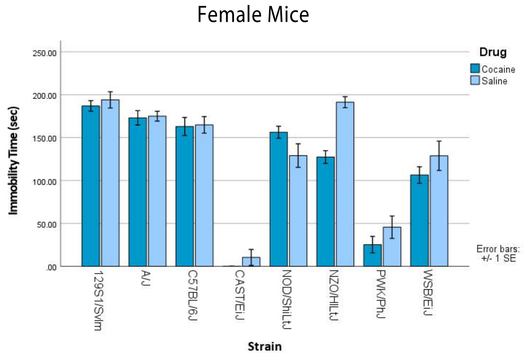


Figure 4. Mean immobility time during the FST for female mice.There was a significant interaction between strain and drug, $F(7, 115) = 2.420$, $p < 0.025$, $\eta_p^2 = 0.145$. There was a main effect of strain, $F(7, 115) = 82.661$, $p < 0.001$, $\eta_p^2 = 0.785$, and a main effect of drug, $F(1, 115) = 5.685$, $p < 0.019$, $\eta_p^2 = 0.054$.

Female Mice

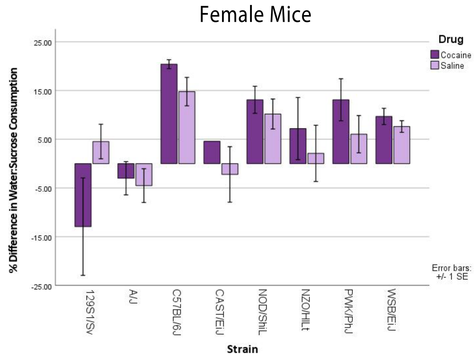


Figure 6. Mean sucrose preference, as measured in the % difference from null (50% consumption of both water and sucrose), for female mice. There was a main effect of strain, $F(7, 63) = 5.172$, $p < 0.001$, $\eta_p^2 = 0.430$.

Discussion

We identified behaviral differences between mice of both sexes on measures of dysphoria- and anhedonia- like behavior.

The effects of cocaine withdrawal on behavior were sex dependent for the FST, including both for latency to immobility and time spent immobile. Female mice exhibited signficant behavioral variations due to withdrawal, while male mice did not.

We did not find significant interactions of cocaine withdrawal on sucrose preference, although there was some evidence of aversion to the sucrose during cocaine withdrawl, seen in enhanced negative percent difference in water to sucrose consumption.

Future Directions

Given that we found few significant effects of cocaine withdrawal on behavior, future work will explore refinment of the cocaine administration paradigm to enhance the effects of drug withdrawal.

The overall aim of this expirimentation is to provide a useful mouse model for genetic mapping of withdrawal-related traits.

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