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Examining Role of Impulsive Action in BXD Mice to Understand Heritability in Drug Addiction

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Heritable Impulsive Action Positively Correlates with DA turnover in the NAc

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Introduction

- Drug addiction has effects that are subject to individual variability. Genetic variation accounts for at least a portion of this variability.
- Research in both humans and animals has shown that reward sensitivity and impulsivity are traits that predict a greater positive response to abusive drugs. There has yet to be evidence found for underlying genetic influences on these traits.
- The Collaborative Cross (CC) recombinant inbred mouse strains, their inbred founders, and the Diversity Outbred (DO) mice that are derived from them are a powerful genetic reference panel that has potential for revealing genetic contributions to drug abuse and related traits. The 8 founder strains of BXD mice examine the heritability of impulsive traits, reward sensitivity, and the genetic correlations between them and addiction-related phenotypes.

Stages

1. Magazine training, inserting nose into the reward magazine led to delivery of Boost (20-21 µL).
2. Hole 3 of 5 illuminated, mice reinforced with BOOST for making a nosepoke (0, 100, or 200 ms) into that aperture. 50 rewards in 2 h.
3. Hole 3 of 5 illuminated, mice reinforced with BOOST for making a nosepoke (100, 200, or 200 ms) into that aperture. 50 rewards in 1 h.
4. Hole 3 of 5 illuminated, mice reinforced with BOOST for making a nosepoke (100, 200, or 300 ms) into that aperture. 50 rewards in 1 h.
5. (Discrimination acquisition): After initiation of a trial via a poke into hole 3 of 5, the two flanking holes were illuminated. Counterbalanced across mice, a response into one of the holes (left or right) gave a Boost reward, while the other resulted in the house lights turning off and a time out period. Criterion: Achieving >=80% response accuracy in a sliding window of 20 trials. Daily sessions lasted 1 h and continued until reaching criterion.
6. (Reversal learning): Much like during stage 5, the center nose hole was lit and the two flanking lights illuminated upon trial initiation. During reversal, however, the opposite nose poke hole was associated with reward, while the previously correct nose poke hole resulted in no reward, lights off, and a time out period. Criterion was same as discrimination acquisition.

Results

Correlations:
TTC and DOPAC turnover: ($r[6]=.886$, $p<.05$)
TTC and DOPAC quantity: ($r[6]=.922$, $p<.01$)

Behavioral:
Main effect of impulsivity on impulsive action ($F[1,50]=15.250$, $p<.001$), with higher impulsive strains requiring more trials overall to meet stage criteria.

Interaction between impulsivity and stage interaction ($F[1,50]=6.495$, $p<.05$), showing that higher impulsive strains took more trials to meet criteria in reversal than they did in acquisition.

No significance on different type of impulsivity through premature responding in both the correct & incorrect hole.

Main effect of impulsivity with higher impulsive strains for correct ($F[1,50]=7.305$, $p<.01$), omissions ($F[1,50]=16.257$, $p<.001$), and trial initiation time ($F[1,50]=5.555$, $p<.05$).

Interaction between impulsivity and stage interaction for trial initiation time ($F[1,50]=.324$, $p>.05$).

No interaction between impulsivity and stage interaction for correct and omit.

Methods

- Mice are bred at Binghamton University

- Strains BXD45, BXD51, BXD56 - high impulsivity
- Strains BXD49, BXD83, BXD90 - low impulsivity

- Testing began when mice were between PND 70 +/- 10

- Mice were placed onto food restriction, and their body weights were lowered to approximately 80% of their free feeding weights, at which point they began testing.
  - All mice underwent 1 d of habituation to the operant chamber (5-hole nose-poke wall chambers; Model MED-NP5M-B1; Med-Associates Inc., St Albans VT).

Figures

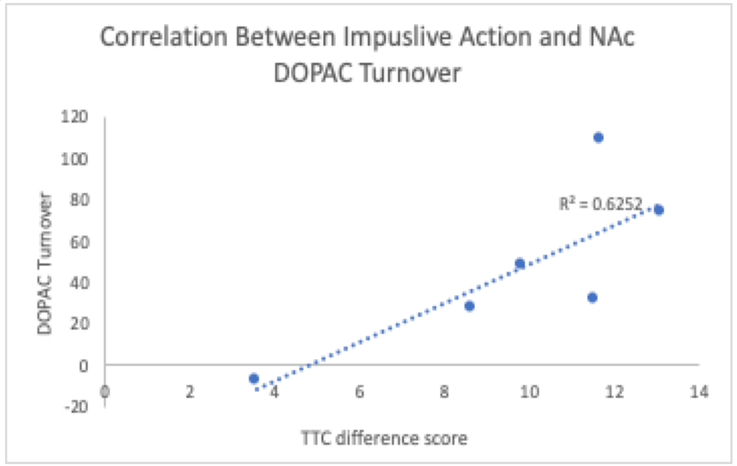

Figure 1. Positive correlation between DOPAC turnover in the NAc and impulsive action ($R^2 = 0.6252$).

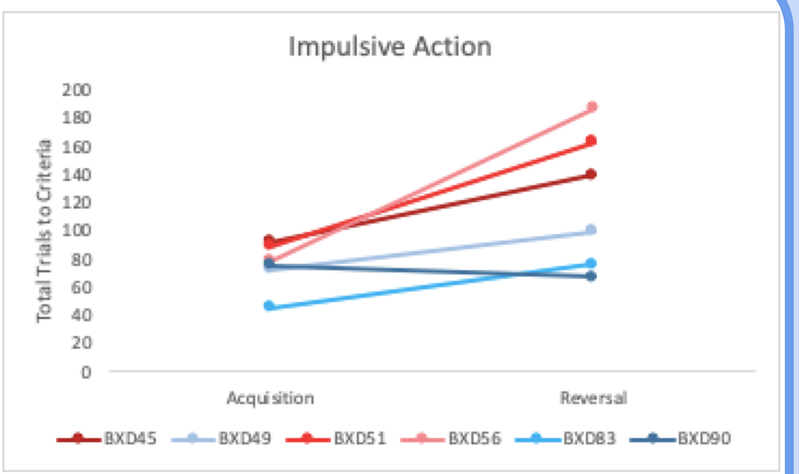

Figure 2. Impulsive action and TTC for all 6 strains from acquisition to reversal.