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Research report

Sex and strain influence attribution of incentive salience to reward cues in mice

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HIGHLIGHTS

- We detected Pavlovian conditioned approach in Collaborative Cross and Diversity Outbred founders.
- Significant strain differences in sign-tracking and goal-tracking were observed.
- Strain differences in sign-tracking and goal-tracking interacted with sex.
- Sign-tracking and novelty reactivity were genetically correlated in males.
- Sign-tracking was robust in some mouse strains.

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ABSTRACT

The propensity to attribute incentive salience to reward cues, measured by Pavlovian sign-tracking, is strongly associated with addiction-related traits including cocaine self-administration, impulsivity, novelty reactivity, and novelty preference. Despite its critical role in addiction, the genetic underpinnings of incentive salience attribution and its relationship to drug addiction are unknown. Mouse genetics can be a powerful means to discover genetic mechanisms underlying this relationship. However, feasibility of genetic dissection of sign-tracking in mice is unknown as only a single study limited to male C57BL/6J mice has rigorously examined this behavior, and limited sign-tracking was observed. Highly diverse mouse populations such as the Collaborative Cross (CC) and Diversity Outbred population (DO) possess a greater range of behavioral and genetic variation than conventional laboratory strains. In the present study, we evaluated sign-tracking and the related phenotype goal-tracking in mice of both sexes from five inbred CC and DO founder strains. Male CAST/EiJ mice exhibited robust sign-tracking; male NOD, male C57BL/6J, and female A/J mice also exhibited significant sign-tracking. Male and female mice from all strains exhibited significant goal-tracking, and significant strain and sex differences were observed. Sign-tracking in males was genetically correlated with exploration of a novel environment, and heritability of sign-tracking and goal-tracking ranged from .32 to .41. These data highlight the importance of considering genetic diversity when evaluating the occurrence of specific behavioral traits in the laboratory mouse and demonstrate that the CC and DO mouse populations can be used to discover mechanisms underlying genetic relationships among sign-tracking and addiction-related behaviors.

1. Introduction

The propensity to attribute motivational properties (i.e., incentive salience) to stimuli which predict reward is a critical component of drug addiction [1]. This phenomenon has been extensively studied in male rats using a Pavlovian conditioned approach (PCA) paradigm in which subjects learn that a conditioned stimulus, such as the extension of a lever, reliably predicts an unconditioned stimulus, such as the delivery of a food pellet [2–4]. Upon lever extension, many rats approach the pellet receptacle to await delivery of the reward, termed goal-tracking (GT). Others, however, approach the lever which signals pellet delivery, termed sign-tracking (ST). The degree to which rats attribute incentive salience to the stimulus that signals reward (i.e., manifest the ST phenotype) is strongly predictive of multiple addiction-related phenotypes (reviewed in [3]) as well as phenotypes which

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predispose individuals to addiction such as impulsivity, novelty reactivity, and novelty preference [5–7]. Although the propensity to attribute incentive salience to reward cues is believed to be a critical component of drug addiction, the genetic underpinnings of incentive salience and its relationship to addiction are unknown. Moreover, the impact of sex on incentive salience attribution has been largely unexplored, even in the rat species [8]. As sex differences in addiction have been widely observed in humans and animal models [9], sex may be a critical variable mediating the genetic relationship between incentive salience attribution and addiction.

Mouse genetics is an effective method for discovering the biological mechanisms driving behavioral variation, including relationships between incentive salience and addiction. Moreover, recently developed genetically diverse experimental mouse populations such as the Collaborative Cross genetic reference panel (CC) and closely related Diversity Outbred population (DO) provide unprecedented opportunities for genetic analysis [10]. However, the feasibility of using the PCA paradigm to identify the genetic underpinnings of incentive salience attribution in mice and the potential impact of sex on this relationship are unknown. This is because only a single study has rigorously examined ST and GT in the mouse species [11], and this study was limited to male mice from the C57BL/6J (B6) strain. Moreover, although Tomie and colleagues (2012) observed significant ST and GT in male B6 mice, the ST observed in that study was markedly less robust than the ST observed in many rat studies; this observation has led some to suggest that the mouse species as a whole is ill-suited for genetic analysis using the PCA paradigm [12]. An alternative explanation, however, is that male mice of the B6 genotype manifest a predominantly GT phenotype, whereas other genotype–sex combinations would manifest a predominantly ST phenotype. To date, this hypothesis has not been tested.

In the present study, we assessed ST and GT using a PCA task in male ($n = 48$) and female ($n = 48$) mice from four common inbred strains (C57BL/6J, 129S1/SvImJ, AJ, NOD/ShiLtJ) and one wild-derived inbred strain (CAST/EiJ). These strains are members of the eight founder strains of the CC and DO genetic mapping populations. To enable dissociation of ST and GT from lever and pellet dispenser approach unrelated to PCA [13], mice were tested on either a paired or an unpaired version of the task. In the paired version, lever extension predicted pellet delivery. In the unpaired version, pellet delivery was randomized. Heritability of ST and GT as well as the genetic correlation of ST with novelty reactivity were also assessed.

2. Materials and methods

2.1. Subjects

Male ($n = 48$) and female ($n = 48$) mice from four common inbred strains [C57BL/6J (B6), 129S1/SvImJ (129), A/J (AJ), NOD/ShiLtJ (NOD)] and one wild-derived inbred strain [CAST/EiJ (CAST)] were tested on the PCA task. These strains represent five of the eight founder strains of the genetically diverse CC [14] and DO [15] mouse populations which we and others have used for high-resolution genetic mapping of complex behavioral traits [16–20]. All mice were acquired from The Jackson Laboratory (stock numbers 000664, 002448, 000646, 001976, and 000928, respectively). Mice were housed in duplex polycarbonate cages and maintained in a climate-controlled room under a standard 12:12 light–dark cycle (lights on at 0600 h). Bedding was changed weekly and mice had free access to acidified water throughout the study. Mice were provided free access to food (NIH31 5K52 chow, LabDiet/PMI Nutrition, St. Louis, MO) until behavioral testing began, at which point they were food restricted such that they weighed 85–90% of base weight when testing commenced each day. Mice were fed immediately following testing. A Nestlet and Shepherd Shack were provided in each cage for enrichment. Mice were housed in same sex groups of 3–5 prior to behavioral testing. Once testing began, mice were housed individually to facilitate food restriction. All procedures and protocols were approved by The Jackson Laboratory Animal Care and Use Committee and were conducted in compliance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

2.2. Apparatus

ST and GT data were collected using 16 Med Associates (St. Albans, Vermont) conditioning chambers (ENV-307W) enclosed in sound attenuating cubicles (ENV-022V). The floor of each chamber consisted of bars which were completely covered by a single piece of acrylic to facilitate cleaning and mouse ambulation. A retractable response lever (ENV-312-2W) was mounted to the left front wall 18 mm above the chamber floor and 28 mm away from the adjacent wall. A pellet dispenser (ENV-203-20) delivered 20 mg Bio-Serv (Flemington, NJ) Dustless Precision Pellets (F0071) into a pellet receptacle (ENV-303W). The receptacle was mounted to the right front wall 3 mm above the chamber floor, 28 mm away from the adjacent wall, and 125 mm away from the lever. A house light (ENV-315W) with bulb (CM1820; Chicago Miniature; Novi, Michigan) was mounted outside and behind the rear wall of the chamber. A monochrome micro video camera (Noldus Information Technology; Leesburg, VA) was mounted to the ceiling of the sound attenuating cubicle directly above the chamber. The camera was connected to a video capture card in a Windows PC (Noldus Information Technology) which was used to record mouse behavior during testing. Conditioning chambers were controlled by a Med Associates control unit using MED-PC IV software. The ST/GT program was written in-house in MEDState notation.

2.3. Pavlovian conditioned approach testing

Prior to testing, mice were randomly assigned to either a paired or an unpaired condition ($n = 9$–10 per strain in each condition, half males and half females). Mice in the paired condition received PCA training in which pellet delivery was paired predictably with lever extension and retraction. Specifically, pellet delivery and lever retraction occurred simultaneously 10 s following lever extension. Mice in the unpaired condition received identical training with the exception that pellet delivery was randomized relative to lever extension and retraction. The house light was illuminated throughout the session. Sessions consisted of 25 trials. Each trial was followed by an inter-trial interval (ITI) of random duration ranging from 30 to 150 s. The lever was extended and retracted at the beginning and end, respectively, of each 10 s trial. For mice in the paired group, a pellet was delivered concurrently with lever retraction. For mice in the non-paired group, a pellet was delivered at a random time between the beginning of each ITI and the end of the subsequent trial. All mice in the study received 25 pellets during each session. Mice were tested between 11 AM and 4 PM. Each chamber was cleaned using 70% ethanol between testing sessions. The number of lever presses and pellet-receptacle head entries during the trial and ITI were recorded automatically on each session by means of infrared detectors built into the levers and pellet receptacles. Because many mice showed evidence of (1) lever contact that did not result in lever depression and (2) shallow pellet-receptacle head entry that did not result in an infrared beam break, the entire session was recorded for all mice on the final testing day (session 15), and video data were subsequently scored to quantify approach