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Research report

Positive and negative feedback learning and associated dopamine and serotonin transporter binding after methamphetamine

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HIGHLIGHTS

- Long-term positive and negative feedback learning was studied after methamphetamine.
- Drug pretreatment resulted in increased use of positive feedback in learning.
- Despite intact negative feedback learning, pretreated rats made more early errors.
- Striatal DAT binding was inversely correlated with positive feedback learning.
- Frontocortical SERT binding was inversely correlated with measures of perseveration.

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ABSTRACT

Learning from mistakes and prospectively adjusting behavior in response to reward feedback is an important facet of performance monitoring. Dopamine (DA) pathways play an important role in feedback learning and a growing literature has also emerged on the importance of serotonin (5HT) in reward learning, particularly during punishment or reward omission (negative feedback). Cognitive impairments resulting from psychostimulant exposure may arise from altered patterns in feedback learning, which in turn may be modulated by DA and 5HT transmission. We analyzed long-term, off-drug changes in learning from positive and negative feedback and associated striatal DA transporter (DAT) and frontocortical 5HT transporter (SERT) binding in rats pretreated with methamphetamine (mAMPH). Specifically, we assessed the reversal phase of pairwise visual discrimination learning in rats receiving single dose- ($mAMPH_{single}$) vs. escalating-dose exposure ($mAMPH_{escal}$). Using fine-grained trial-by-trial analyses, we found increased sensitivity to and reliance on positive feedback in mAMPH-pretreated animals, with the $mAMPH_{single}$ group showing more pronounced use of this type of feedback. In contrast, overall negative feedback sensitivity was not altered following any mAMPH treatment. In addition to validating the enduring effects of mAMPH on early reversal learning, we found more consecutive error commissions before the first correct response in mAMPH-pretreated rats. This behavioral rigidity was negatively correlated with subregional frontocortical SERT whereas positive feedback sensitivity negatively correlated with striatal DAT binding. These results provide new evidence for the overlapping, yet dissociable roles of DA and 5HT systems in overcoming perseveration and in learning new reward rules.

1. Introduction

Learning from mistakes and prospectively adjusting behavior in response to negative feedback is an important facet of performance monitoring. This cognitive process has been shown to get poorer with age [1,2] and is also suboptimal in youth with a history of disruptive behavior [3]. Recent evidence shows that "high learners" utilize errors (or negative feedback) more optimally to update their future reward choices [4]. A plentitude of rodent and non-human primate research shows that such integration of feedback occurs via heterogenous reward signals in the prefrontal cortex, and that learning from both positive and negative feedback depends on dopamine (DA) signaling in areas like the orbitofrontal cortex (OFC) and basal ganglia [5]. Not surprisingly DA drugs, such as those given to Parkinson's patients, have been shown to modulate learning from reward feedback [6].

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Chronic exposure to cocaine or methamphetamine (mAMPH) results in progressive and long-lasting changes in the mesencephalic DA system [7–11]. Repeated administration of high doses of mAMPH results in long-lasting reductions in total DA content [12–14], reduced activity of tyrosine hydroxylase [15,16], decreased DA transporter binding and density [17–21], and compromised DA D2-like receptor availability in the striatum [22]. MAMPH administration also produces enduring impairments in cognitive flexibility, when the inhibition of previously-learned responses is required. Animal models of mAMPH addiction provide evidence that pathological neuroplasticity in prefrontal cortex and striatum underlie compulsive drug seeking and relapse [23–25]. Collectively, the preceding evidence strongly emphasizes the role of DA pathways in feedback-guided learning and suggests that some of the impairments induced by drug exposure as well as the vulnerability to the development of compulsive drug use may arise from altered patterns in feedback monitoring.

Several groups have analyzed how animals use positive and negative trial-by-trial feedback [26–29], however these parameters have not been previously explored in pharmacological studies. Additionally, to our knowledge the effects of different mAMPH administration regimens on animals' responses to reward feedback have not been previously examined. Both single-dose exposure ($mAMPH_{single}$) and escalating exposure to mAMPH ($mAMPH_{escal}$) result in cognitive flexibility impairments, as measured by attenuated reversal learning [30]. Though these regimens of mAMPH treatment produce remarkably similar learning impairments, the DA system may be differentially affected and produce such impairments through unique mechanisms. In the present experiment we compared $mAMPH_{escal}$, $mAMPH_{single}$, and saline (SAL)-treated animals on measures of feedback learning. Specifically, we assessed sensitivity to reward feedback or omission of anticipated reward on the reversal phase of pairwise visual discrimination learning. It should be noted that the trial-by-trial feedback learning we analyzed here occurred well outside of a drug wash out period and do not represent acute effects of mAMPH. Any changes we observed in performance monitoring therefore, represent enduring effects of the drug on this cognitive process.

2. Materials and methods

2.1. Subjects

Previously-collected and published data [30] were reanalyzed in the present study for trial-by-trial feedback performance. Twenty-one male Long–Evans rats (Charles River Laboratories, Raleigh, NC) weighing between 275 and 300 g at the beginning of the study were individually housed during food restriction, given water ad libitum and maintained at a 12-h light/12-h dark cycle, with the temperature at 22 °C. Body weights were monitored daily. Behavioral testing took place between 0800 and 1600 h during the rats' inactive period, consistent with previous studies in our lab [30,31]. All procedures were in accordance with the Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee at California State University, Los Angeles.

2.2. Food restriction and acclimation to food rewards

When rats reached a minimum body weight of 275 g, they were food restricted to no less than 85% of their free-feeding body weight to ensure motivation to work for food, while water was available ad libitum. On each of the two days prior to the start of testing, rats were fed 20 sucrose pellets in their home cage to accustom them to the food reward.

2.3. Apparatus

Operant conditioning chambers [35 cm (length) × 28 cm (width) × 34 cm (height)] (#80004, Lafayette Instrument Co.) were housed within sound- and light-attenuating cubicles (#83018DDP, Lafayette Instrument Co.). Each chamber was equipped with an LCD touchscreen (Elo Touch). The houselight was located adjacent to the touchscreen, whereas the tone generator and pellet tray were located next to the pellet dispenser, opposing the touchscreen. The pellet dispenser delivered single 45 mg dustless sucrose pellets (BioServ). Custom software (Ryklin Software Inc.) was used.

2.4. General

The animals were given one testing session per day until the learning criterion was reached and were restricted to a maximum of 60 correct responses or 120 total trials per testing session. Each session of training and testing lasted a maximum of 45 min. Only a small area (2.5 cm diameter circle) on the touchscreen was sensitive to nosepoking, while all other areas were programmed to be unresponsive. The primary parameter considered for advancement in learning was *performance accuracy*, defined as percent correct (correct/total trials). Criterion in each phase of pretraining was 60 correct nosepokes at 85% correct responses to the stimulus within 45 min, on each of two consecutive days. The testing session was terminated for one of the three reasons: (1) allotted time had elapsed, (2) maximum number of trials had been reached, or (3) maximum number of correct responses had been reached.

2.5. Autoshaping and pretraining

Autoshaping began with the display of white graphic stimuli on the black background of the touchscreen, the disappearance of which coincided with the onset of a "reward event": a sucrose pellet, a 1 s tone, and a 1 s illumination of the house light. An ITI of 20 s was used, while stimuli remained on the screen for 8 s. At any time, rats could nosepoke the stimuli on the touchscreen and initiate the reward event. Criterion for autoshaping occurred when rats ate 60 sucrose pellets within 30 min for each of two consecutive days. After autoshaping, the pretraining phase commenced and consisted of four different stages previously outlined in detail [30].

2.6. Visual discrimination learning

Rats were presented with two novel, white, equiluminescent stimuli that differed only in shape [32,33] with predetermined reinforcement contingencies. The software enabled either a reward event as a result of nosepoking the correct stimulus (S+), or a punishment as a result of nosepoking the incorrect stimulus (S−); the latter consisting of a 5 s "houselight off" and "time out" wherein rats were unable to initiate the next trial. If the rat committed an error and received a punishment, a correction trial was administered: this consisted of the same left/right presentation of the stimulus until the rat nosepoked correctly. These were consecutive errors and were tallied independently of "first" errors. Stimuli presentation (i.e. left/right presentation of the S+) occurred pseudorandomly according to a Gellerman schedule. Stimulus assignment (S_A+S_B- or S_A-S_B+) was counterbalanced across treatment groups.

2.7. Drug treatment

Rats were given injections of mAMPH (Sigma, St. Louis, MO; s.c.) or physiological SAL solution (1 ml/kg, s.c.) on a clean room procedure table in their housing room, five times per week for 4 weeks, between 1200 and 1500 h. A 4-week treatment regimen