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Instrumental learning in hyperdopaminergic mice

Henry H. Yin [a,*], Xiaoxi Zhuang [b], Bernard W. Balleine [c]

[a] *Section of Synaptic Pharmacology, Laboratory for Integrative Neuroscience, NIAAA/NIH, Bethesda, MD 20892, USA*
[b] *Department of Neurobiology, Pharmacology and Physiology, The University of Chicago, Chicago, IL 60637, USA*
[c] *Department of Psychology and Brain Research Institute, UCLA, Los Angeles, CA 90092, USA*

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Abstract

In two experiments we investigated the effects of elevated dopaminergic tone on instrumental learning and performance using dopamine transporter knockdown (DAT KD) mice. In Experiment 1, we showed that both DAT KD mice and wild-type controls were similarly sensitive to outcome devaluation induced by sensory specific satiety, indicating normal action–outcome learning in both groups. In Experiment 2, we used a Pavlovian-to-instrumental transfer procedure to assess the potentiation of instrumental responding by Pavlovian conditional stimuli (CS). Although during the Pavlovian training phase the DAT KD mice entered the food magazine more frequently in the absence of the CS, when tested later both groups showed outcome-selective PIT. These results suggest that the elevated dopaminergic tone reduced the selectivity of stimulus control over conditioned behavior, but did not affect instrumental learning.

Keywords: Dopamine; Dopamine transporter; Learning; Instrumental conditioning; Operant; Inhibitory control

1. Introduction

Dopamine (DA) has a variety of effects on cortico-basal ganglia circuits. It is critical for the acquisition and modification of adaptive, purposive behaviors, though its effect at the level of neural systems remains controversial (Robinson & Berridge, 2003; Schultz, 1998a; West, Floresco, Charara, Rosenkranz, & Grace, 2003). In recent years, the role of DA in instrumental learning has also attracted much attention (Reynolds, Hyland, & Wickens, 2001; Wickens & Koetter, 1995; Wickens, Reynolds, & Hyland, 2003). According to a popular account, DA serves to stamp in associations between stimulus and response during instrumental conditioning by facilitating heterosynaptic long-term plasticity in the striatum (Wickens et al., 2003). In support of this claim, it has been shown that DA innervation of the sensorimotor striatum is necessary for habit formation in instrumental conditioning (Faure, Haberland, Conde, & El Massioui, 2005). In vitro studies using brain slices have also demonstrated a critical role for DA in striatal plasticity (Kerr & Wickens, 2001; Lovinger, Partridge, & Tang, 2003).

Studies using either the water maze or the radial arm maze have also shown that the dorsal striatum plays a major role in tasks (e.g., win-stay) in which a discrete stimulus signals the location of the food and the response to be performed (Devan, McDonald, & White, 1999; Devan & White, 1999; Packard & McGaugh, 1992). More importantly, local injection of dopamine agonists into the dorsal striatum appears to enhance the acquisition of these tasks, suggesting a role for striatal dopamine in habit learning (Packard & White, 1991).

The idea that DA serves as the reinforcement signal in S–R habit learning is particularly interesting in light of the growing body of work in defining the neural substrates of instrumental learning. This work has shown that two largely independent neural systems control the learning and performance of instrumental actions such as lever pressing (Corbit & Balleine, 2003; Corbit, Muir, & Balleine, 2003; Yin, Knowlton, & Balleine, 2004, 2005a, Yin, Ostlund, Knowlton, & Balleine, 2005b). Initially, as animals learn to

* Corresponding author.
E-mail address: yinh@mail.nih.gov (H.H. Yin).

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press the lever for food, they encode the specific relationship between their actions and the rewarding outcomes, and their behavior is controlled by encoded action–outcome associations. This action–outcome learning depends on the associative cortico-basal ganglia network, particularly that involving the dorsomedial striatum (Yin, Knowlton, & Balleine, 2005a, 2005b). After extended training, however, instrumental actions can become habitual, i.e., controlled by antecedent stimuli rather than by outcome expectancy (Dickinson & Balleine, 1993). This more gradual process of habit formation appears to depend on the sensorimotor cortico-basal ganglia network, particularly the dorsolateral striatum (Yin et al., 2004) and dopaminergic afferents to this area (Faure et al., 2005).

The present study used dopamine transporter knockdown (DAT KD) mice to assess the contribution of tonic DA to instrumental learning and performance. After release, DA is rapidly taken up by the high-affinity DAT, a protein expressed exclusively in brain regions where DA is synthesized (West et al., 2003). The DAT KD mice, which develop normally, have a 70% higher level of tonic DA, thus providing a useful tool for examining the effects of enhanced tonic DA on striatum-dependent learning (Pecina, Cagniard, Berridge, Aldridge, & Zhuang, 2003; Zhuang et al., 2001).

In particular, we tested the hypothesis that S–R habit learning might be enhanced in these hyperdopaminergic animals. If tonic DA is critical for habit learning, then given the same amount of training the instrumental performance of DAT KD mice should be predicted to be less sensitive to outcome devaluation than WT controls. Furthermore, given the evidence that habits depend for their performance on the motivating aspects of reward-related cues (Holland, 2004), instrumental performance in the DAT KD mice should be predicted to show increased sensitivity to the excitatory effects of Pavlovian cues. These two predictions were assessed in Experiments 1 and 2, respectively.

2. Methods

2.1. Experiment 1: Instrumental learning

2.1.1. Subjects and apparatus

Eight wild-type mice and 6 KD mice (all males) were used for both experiments. The generation of DAT KD mice has been described in an earlier paper (Zhuang et al., 2001). Training and testing took place in 7 Med Associates (East Fairfield, VT) operant chambers housed within sound- and light-resistant walls. Each chamber was equipped with a pump fitted with a syringe that could deliver sucrose solution into a recessed magazine in the chamber, as well as a pellet dispenser that can deliver food pellets into the same magazine. The chambers also contained two retractable levers, which could be inserted to the left and right of the magazine. A 3 W, 24 V house light mounted on the top-center of the wall opposite the magazine provided illumination. Microcomputers equipped with the MED-PC program (Med Associates, VT) controlled the equipment and recorded the lever-presses.

2.1.2. Instrumental training

All mice were placed on a food deprivation schedule to reduce their weight to about 90% of their free-feeding weight. Body weights were maintained by adjusting the amount of food given each day. All mice were fed approximately 2 h after behavioral training and testing were completed each day. Water was always available in the home cages.

The food rewards used were pellets (20 mg, Bio-serv, New Jersey) and 0.02 ml of 20% sucrose solution. The pre-training phase began with two 30-min magazine training sessions in which the reinforcers were delivered on a random time 60 s schedule without the levers, allowing the mice to learn the location of food delivery. Lever-press training began the next day. On each day, all mice were given two sessions, one for each lever. For half of the mice, the left lever earned pellets, and the right lever earned sucrose; for the other half, the opposite action–outcome contingency was assigned. Each session began with the illumination of the house light and insertion of the lever and ended after 30 reinforcers had been earned, with the retraction of the levers and turning off of the house light. There was a 1-h break between the two sessions. Progressively leaner schedules of reinforcement were used: 4 days of continuous reinforcement (CRF), 1 day of random ratio-5 (RR-5, i.e., each response was rewarded at a probability of 0.2), and 1 day of RR-10, and 3 days of RR 20.

2.1.3. Outcome devaluation

After the 9 days of lever press training, half of the mice in each action–outcome assignment received 20 g of pellets in a bowl, and the remaining mice received 20 ml of sucrose solution in a drinking tube in their home cages. Immediately thereafter, they were given a 5-min choice extinction test. The test began with the illumination of the house light and insertion of both levers, and ended with the retraction of the levers and the offset of the house light. No reinforcer was delivered during this test.

2.2. Experiment 2: Pavlovian-to-instrumental transfer

After the completion of experiment 1, the same mice were used in Experiment 2. They received 5 daily sessions of appetitive Pavlovian conditioning. During each session, two stimuli (offset of the house light and a 85 dB, 2000 Hz tone) served as conditional stimuli (CS) and were paired with either pellet or sucrose delivery. For half the animals in each genotype, tone was paired with pellet, and darkness was paired with sucrose. The remaining half received the opposite pairings. Four presentations of each stimulus were given in each session interspersed with periods (5-min on average) in which no stimuli were presented. The stimulus presentations were 2 min in duration during which the reward was delivered on a RT-30 s schedule. The number of head entries into the food magazine during the CS as well as a pre-CS interval of 2 min was measured.

The animals received two extinction tests (one on each lever and one day apart). During each test one of the levers was available and each 2-min stimulus was presented 4 times interspersed with intervals of equal duration with no stimulus. Each test was 40 min long, and began with 8 min of extinction on the lever to reduce baseline responding, followed by 8 stimulus trials (4 for each CS) and 8 no-stimulus inter-trial intervals.

3. Results

3.1. Enhanced motivation but normal acquisition of action–outcome learning

During the initial acquisition phase (Fig. 1A), both groups rapidly increased lever pressing over sessions. The acquisition of lever pressing for each reinforcer over 9 days of training was analyzed with a mixed two-way ANOVA. For pellets, there was a main effect of days ($F_{8,12} = 25.2$, $p < .05$), no main effect of genotype ($F_{1,12} = 2.0$, $p > .05$), and no significant interaction between days and genotype ($F_{8,12} = 1.54$, $p > .05$). For sucrose, there was a main effect of days ($F_{8,12} = 15.1$, $p < .05$), no main effect of genotype ($F_{1,12} = 1.8$, $p > .05$), and no significant interaction between

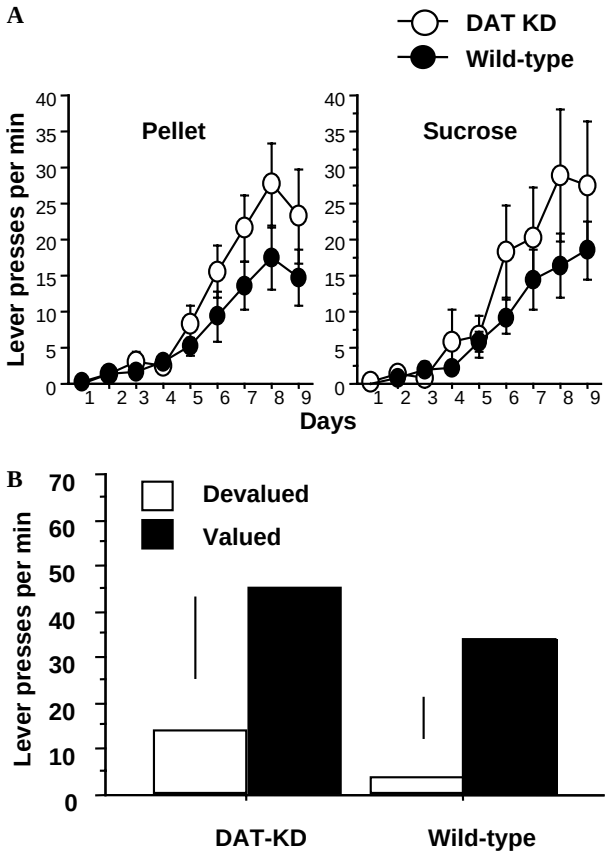

Fig. 1. Instrumental learning. (A) Acquisition of lever pressing. Left panel, lever pressing for pellets; right panel, lever pressing for sucrose. Wild-type: $n = 8$; DAT KD: $n = 6$. (B) Performance on the outcome devaluation test, conducted in extinction. Devaluation is measured by comparing, within each subject, response rate on the lever earning the devaluated outcome and that on the lever earning the non-devalued outcome. Each vertical line represents one SED (standard error of the difference of the means).

days and genotype ($F_{8,12} = 1.0$, $p > .05$). Both DAT KD and WT mice were thus able to learn to acquire the actions, though the DAT KD groups showed numerically higher response rates.

Although the DAT KD mice responded at numerically higher rates (which did not reach statistical significance) than the WT mice, there is no evidence that they acquired instrumental learning at a faster rate. As shown in Fig. 1B, when the degree to which performance was controlled by the action–outcome association was assessed using an outcome devaluation test, it appeared that the DAT KD and WT mice were similarly sensitive to this manipulation.

A mixed two-way ANOVA showed a main effect of devaluation ($F_{1,12} = 6.13$, $p < .05$), no main effect of genotype ($F_{1,12} = 1.47$, $p > .05$), and no interaction between genotype and devaluation ($F < 1$). The performance of both DAT KD and WT mice was sensitive to outcome devaluation, selectively reducing responding on the lever that earns the devalued outcome. Both groups appeared similarly to acquire lever pressing as a goal-directed action directly controlled by the expectancy of the specific outcomes.

3.2. Pavlovian training

The data from the 5-day Pavlovian training phase are shown in Fig. 2A. As is clear from this figure, although WT mice showed clear discrimination between the CS and preCS periods throughout training, the DAT KD mice did not. Both groups showed similar levels of performance to the Pavlovian cues, suggesting that excitation to these cues was similar in both groups. The DAT KD mice appeared unable to inhibit their performance of magazine approach during the pre-CS periods. A mixed three-way ANOVA revealed main effects of genotype ($F_{1,12} = 5.56$, $p < .05$), of days ($F_{4,12} = 7.9$, $p < .01$), of stimulus ($F_{1,12} = 41.3$, $p < .01$), and only a significant interaction between stimulus and genotype ($F_{1,12} = 5$, $p < .05$). Further analysis showed that for WT mice, there was a main effect of stimulus($F_{1,12} = 75.6$, $p < .01$), but not for the DAT KD mice ($F_{1,12} = 4.83$, $p = .08$). Thus, whereas the WT mice responded more during the CS than during the pre-CS period, the DAT KD mice showed attenuated discrimination between the pre-CS and the CS periods.

3.3. Pavlovian-to-instrumental transfer

Transfer is measured as the change in response rate during the CS compared to the pre-CS period. Both DAT KD and WT mice significantly increased responding from the pre-CS baseline on the lever that, during training, earned

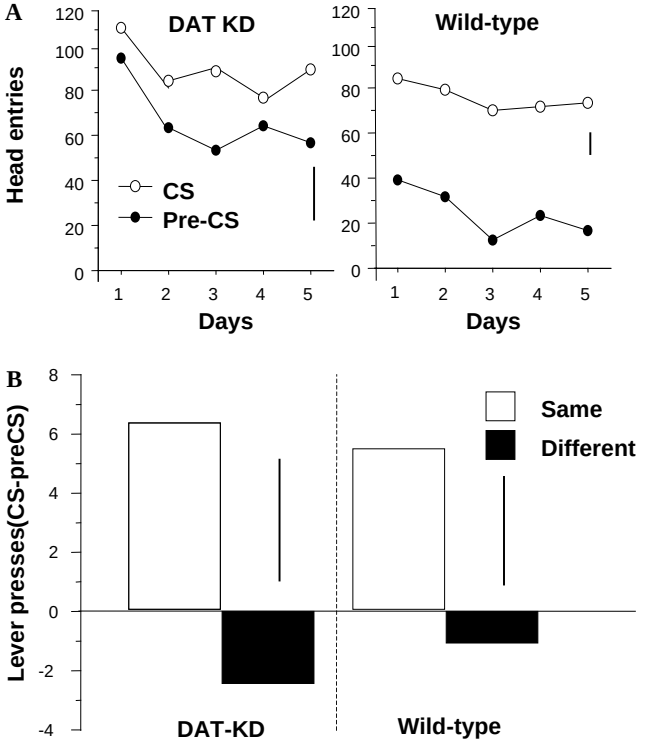

Fig. 2. Pavlovian-to-instrumental transfer test. (A) Head entries (CRs) during Pavlovian training. (B) Potentiation of lever pressing during transfer test conducted in extinction. Each vertical line represents one SED (standard error of the difference of the means).

the same food reward as that signaled by the CS; but they did not increase responding on the control lever, i.e., the lever that in training delivered an outcome that differed from that signaled by the CS. Furthermore, this specific excitatory effect of the Pavlovian CSs on instrumental performance appeared to be similar in the two groups, suggesting that motivation exerted by the anticipation of specific reward-related cues was not affected in the DAT KD mice. This was indicated statistically by a significant main effect of lever (i.e., Same vs. Different; $F_{1,12} = 6.33$, $p < .05$). Furthermore, there was no main effect of genotype ($F < 1$), nor any interaction between these two factors ($F < 1$).

4. Discussion

Experiment 1 assessed the content of instrumental learning in DAT KD mice using outcome devaluation, the canonical assay for detecting action–outcome encoding. Both DAT KD mice and their WT controls were able to acquire two actions each earning a different outcome. It should be noted that the instrumental training procedure used in this study is specifically designed to generate considerable sensitivity to outcome devaluation in the performance of the controls.

Although DAT KD mice showed numerically higher response rates (Fig. 1A), their instrumental learning appeared similar to that of the control mice: When one of the rewards was devalued by pre-feeding before a probe test of learning (conducted in extinction), both groups selectively reduced responding on the lever that, in training, earned the now-devalued reward (Fig. 1B). This pattern of response distribution across two levers indicates that the KD mice and the wild-type controls were both able to recall the specific action–outcome contingency, i.e., which action leads to which outcome. We therefore conclude that enhanced tonic DA has no effect on action–outcome learning. Nor does it appear to increase habit learning, since no evidence was found of a *reduction* in sensitivity to devaluation in DAT KD mice, a pattern that would have indicated enhanced habit learning. Nevertheless, the present results cannot rule out the possibility of differential sensitivity to devaluation given more extensive training or training under different reinforcement schedules.

Experiment 2 assessed the extent to which a Pavlovian conditional stimulus, established as a predictor of one or the other instrumental outcome, could selectively potentiate performance on the lever that earned the predicted reward in training. As previous research has demonstrated, the ventral striatum, in particular the shell of the nucleus accumbens, is critical for such transfer of incentive motivation from Pavlovian predictors to the system mediating goal-directed actions (Corbit, Muir, & Balleine, 2001). Recent evidence also suggests that DA is necessary for PIT (Dickinson, Smith, & Mirenowicz, 2000). Nevertheless, as shown in Fig. 2B, DAT KD mice and WT controls showed comparable performance on the PIT test. It should be emphasized that, for both groups, the transfer of incentive motivation was selective, i.e., restricted to the specific instrumental action that earns the specific outcome.

An interesting feature of the PIT results is that, during Pavlovian training, the DAT KD mice showed a deficit in the selectivity of cue control over the performance of the CR and entered the food magazine during the pre-CS period as frequently as during the CS period. In contrast, WT mice showed clear discrimination, entering more frequently during the CS than the pre-CS period. As no reward was presented during the pre-CS period, this might be interpreted as a deficit in Pavlovian learning in the DAT KD mice. However, the PIT test conducted later showed that this was not the case; the DAT KD mice showed outcome-specific transfer, indicating that they had in fact learned which CS predicted which reward. This pattern suggests that the DAT KD are less sensitive to the extinction contingency imposed during the pre-CS period, probably because they were more compulsive in entering the magazine (Pecina et al., 2003). Interestingly, previous work has established a similar dissociation between Pavlovian and instrumental performance. For instance, outcome devaluation or Pavlovian extinction does not affect the ability of a CS paired with that outcome to potentiate instrumental responding (Delamater, 1996; Holland, 2004). In the current study, the converse was found—although DAT KD mice did not respond above the pre-CS baseline during the paired stimulus in Pavlovian training, they nevertheless showed selective transfer, i.e., increased performance on the lever that in training had delivered the same outcome as that predicted by the CS.

Since the DAT KD mice did not show enhanced selective PIT, this transfer effect appears to be independent of tonic DA level. Given that DAT KD mice can still release dopamine phasically (Zhuang et al., 2001), one possible mechanism for PIT, which appears to require DA (Dickinson et al., 2000), is phasic signaling via the spiraling striatum–midbrain–striatum circuitry, which allows information from one cortico-basal ganglia circuit to be transferred to another (Dickinson et al., 2000; Haber, Fudge, & McFarland, 2000). In the nucleus accumbens, a critical neural substrate for PIT, phasic DA can probably enhance the excitability of the projection neurons (Ghitza, Fabbricatore, Prokopenko, & West, 2004; Nicola, Surmeier, & Malenka, 2000). Alternatively, it is possible that this effect of DA in potentiating transfer is limited to the general excitatory effects of Pavlovian cues with the more specific motivational effects mediated by some other processes (Corbit & Balleine, 2005).

Our results are in accord with and extend those from previous work (Packard & White, 1991; Pecina et al., 2003). In particular, Pecina et al. (2003) showed enhanced acquisition in DAT KD mice on a runaway task, but normal orofacial "liking" reactions to the rewards themselves. It was concluded that enhanced tonic DA in these mice resulted in enhanced "wanting" but normal "liking." In the present study we also found evidence for enhanced incentive motivation, as shown by slightly elevated rates of responding

during acquisition and, more importantly, by the failure to refrain from entering the magazine during the pre-CS period during Pavlovian training. Although this pattern in itself might suggest enhanced instrumental learning accompanied by a deficit in Pavlovian learning, the devaluation and PIT tests revealed that, in fact, the underlying learning was intact in these mice, and that the differences between DAT KD mice and wild-type mice can be attributed to a difference specifically in performance. This conclusion is worth emphasizing, for just as outcome devaluation is designed to assess learning given unequal levels of instrumental performance (lever pressing), so PIT is designed to probe Pavlovian learning when a direct measure of the CR (head entry) could be contaminated by performance factors.

To summarize, despite a 70% increase in DA tone (Zhuang et al., 2001), the DAT KD mice did not show enhanced habit learning and, like the WT controls, showed sensitivity to outcome devaluation and normal outcome-specific PIT. Nor did they show enhanced action–outcome learning. If tonic DA does not play a significant role, then this suggests that the phasic signal may be more crucial in instrumental learning. This conclusion agrees with the available evidence on the activity of DA neurons during behavior. Phasic DA release, presumably as a result of burst firing of DA neurons, is thought to encode the difference between expected and actual reward (Schultz, 1998b). Work by Schultz and colleagues using appetitive Pavlovian conditioning in monkeys has shown a correspondence between the phasic DA signal and a key prediction error posited by theoretical learning models such as the Rescorla–Wagner model and the formally equivalent temporal difference reinforcement learning algorithm (Schultz & Dickinson, 2000; Suri & Schultz, 2001; Waelti, Dickinson, & Schultz, 2001). Recent studies also suggest the involvement of phasic activity of DA in instrumental learning (Bayer & Glimcher, 2005; Kawagoe, Takikawa, & Hikosaka, 2004; Morris, Arkadir, Nevet, Vaadia, & Bergman, 2004; Takikawa, Kawagoe, & Hikosaka, 2004). The DA neurons from the substantia nigra pars compacta, projecting to the dorsal striatum, are probably the major source of phasic DA signals involved in instrumental learning, and the available evidence indicates that here too phasic DA activity encodes a prediction error in tasks that are, at least procedurally, instrumental in nature (Bayer & Glimcher, 2005). Whether such a prediction error, as proposed by a recent theoretical model (Dayan & Balleine, 2002), is necessary for instrumental learning, remains to be assessed by future studies.

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