

Research report

# Inactivation of dorsolateral striatum enhances sensitivity to changes in the action–outcome contingency in instrumental conditioning

Henry H. Yin<sup>a,\*</sup>, Barbara J. Knowlton<sup>b</sup>, Bernard W. Balleine<sup>b</sup>

<sup>a</sup> *Laboratory for Integrative Neuroscience, NIAAA/NIH, 5625 Fishers Lane, Room TS-13, Rockville, MD 20852, USA*

<sup>b</sup> *Department of Psychology and Brain Research Institute, University of California, Los Angeles, USA*

Received 25 May 2005; received in revised form 28 July 2005; accepted 28 July 2005

Available online 8 September 2005

## Abstract

Actions become compulsive when they are no longer controlled by their consequences. Compulsivity can be assessed using the omission procedure in which animals are required to withhold a previously reinforced action to earn reward. The current study tested the hypothesis that inactivation of the dorsolateral striatum (DLS), a structure implicated in habitual behavior, can enhance sensitivity to changes in the action–outcome contingency during omission training, thus leading to a reduction in compulsive responding. Over 10 days rats were trained to press a freely available lever for sucrose reward delivered on interval schedules of reinforcement. After learning to press the lever at a stable and high rate, rats in the omission group received a session in which the rewards were now delayed by pressing the lever; i.e. withholding lever pressing resulted in increased access to reward. A control group was yoked to the omission group and received the same number and pattern of reward delivery but without the omission contingency. Half the rats in each group received infusions of vehicle into the DLS prior to this training whereas the remainder received an infusion of the GABA-A receptor agonist muscimol. On the next day, the effect of these treatments was assessed on a probe test in which the tendency of the various groups to press the lever was assessed in extinction and without drug infusion. Rats that received vehicle infusions prior to the omission session showed complete insensitivity to the newly imposed omission contingency. In contrast, rats given the infusion of muscimol selectively reduced lever pressing compared to yoked controls. Thus, extended training with interval schedules resulted in compulsive lever pressing that prevented the learning of the omission contingency, whereas inactivation of the DLS appeared to enhance the rats' sensitivity to this change in the action–outcome contingency.

© 2005 Elsevier B.V. All rights reserved.

**Keywords:** Basal ganglia; Compulsive behavior; Striatum; Instrumental conditioning; Operant learning; Procedural learning; Habit; Omission

Instrumental control refers to the control of actions by their consequences. It was not until recent decades that effective behavioral procedures were developed for the assessment of such control [8]. One fundamental procedure is called omission, which reverses the causal relation between action and reward [10]. After being trained to press a lever for food, omission training is given in which the food is now delivered when the rat refrains from responding and omitted when the lever is pressed. In this situation the degree of response suppression controlled by this new contingency is measured against a yoked control that receives the same exposure to

the food as the omission group but without the omission contingency. Using this assay, it has been found that omission usually causes a radical reduction in the performance of instrumental actions such as lever pressing [10].

Under certain conditions, however, most notably after habit formation, sensitivity to an omission contingency (and other procedures which reduce the action–outcome contingency) can be attenuated [16,18]. In particular, the schedule of reinforcement used during the initial training phase is a critical manipulation. Two classes of such schedules are commonly used. In ratio schedules, each response is rewarded according to a fixed or variable probability. By contrast, in interval schedules, only the first response after a scheduled time interval is rewarded. As established by previous studies, interval schedules of reinforcement can generate

\* Corresponding author. Tel.: +1 11 301 443 3769; fax: +1 11 301 480 0466.

E-mail address: [yinh@mail.nih.gov](mailto:yinh@mail.nih.gov) (H.H. Yin).

habitual behavior that is insensitive to outcome devaluation [11,17,18,44]. A direct, well-controlled comparison of the schedules demonstrated that, even with the amount of reinforcement equated, interval schedules produce habitual responding whereas ratio schedules do not [17].

Contemporary theories of instrumental conditioning attribute such loss of instrumental control during the course of training to the formation of a stimulus–response (S–R) association; because the outcome is not part of the associative structure of the habit, such behavior is thus expected to render performance insensitive to outcome devaluation and manipulations of the action–outcome contingency [8,15–17].

In recent years, with growing interest in the study of addiction and other disorders involving compulsive behavior, the neural basis of the loss of instrumental control seen in habit formation has become a focus of research. Previous work on addiction has for instance focused on resistance to extinction [40]. As some have proposed, the inflexibility and compulsivity observed in these disorders could be attributed to the potentiation of a stimulus–response (S–R) habit system, which mediates responses elicited by antecedent stimuli independently of the instrumental contingency between the action and outcome [6,19].

The dorsolateral striatum (DLS), the equivalent of the putamen in primates, receives input from the primary sensorimotor cortices and send projections that can ultimately influence brainstem motor control networks as well as the thalamocortical network. This area has been shown by a variety of studies to be an important component of the neural circuitry mediating habitual behavior [3,12,22,24,35]. In a recent study [44], we examined the role of the DLS in habit formation using outcome devaluation, a well-established assay that can detect S–R habits. We found that, whereas the performance of the control rats was insensitive to devaluation of the food reward induced by independent lithium chloride pairing, that of the rats with lesions of the DLS was sensitive to devaluation. In other words, lesion of the DLS resulted in the acquisition of the lever-press response as a goal-directed action, even under training conditions that generated habits in control animals.

The role of the DLS in the acquisition of habitual behavior is of particular interest in the context of overall striatal functioning. Indeed, many studies have found considerable functional heterogeneity within the striatum [4,5,9,12,13,42,43,45]. For instance, within the dorsal striatum (or neostriatum) the dorsomedial region (the counterpart of the caudate nucleus in primates) is involved in place learning and flexible reversal learning [38,39,43]. This important distinction between medial and lateral regions of the dorsal striatum raises questions regarding possible interactions between these regions and, more generally, between two overlapping networks of which these two regions are the striatal components. In a series of previous studies [45,46], we have shown the posterior part of the dorsomedial striatum is indeed critical for the instrumental control over behavior: lesion or inactivation of this area results in habitual behav-

ior even when the training procedure generates goal-directed behavior in control animals. Such results suggest that the dorsomedial striatum, and cortical and pallidal structures within the same cortico-basal ganglia network, play a critical role in the acquisition and performance of goal-directed actions that are sensitive to outcome devaluation and changes in the action–outcome contingency.

In this study, we tested the hypothesis that inactivation of the DLS during omission training would lead to the engagement of the alternative neural system controlling goal-directed actions, thereby enhancing the inhibitory instrumental control of compulsive behavior. Previous work has shown that the kind of extended lever-press training that generated insensitivity to outcome devaluation can also generate insensitivity to the omission contingency [18]. We gave rats extensive training using an interval schedule, which has been shown to result in habitual responding [44]. We predicted that rats receiving vehicle infusions would not decrease responding after omission training compared to their yoked controls, whereas rats receiving muscimol infusions would decrease responding relative to their yoked controls.

## 1. Materials and methods

### 1.1. Subjects and apparatus

Thirty-two naïve male Long-Evans rats weighing between 450 and 510 g were housed singly, maintained on a 14:10 h light–dark cycle, and handled daily for one week prior to surgery. Training and testing took place in 16 Med Associates (Vermont) operant chambers, each equipped with a pump with a syringe which delivered 0.1 ml of 20% sucrose solution into a recessed magazine, and a house light mounted on the wall opposite of the food magazine. Computers equipped with the MED-PC program controlled the equipment and recorded the lever-presses and head entries into the magazine.

### 1.2. Surgery and histology

Rats were anesthetized with sodium pentobarbital (Nembutal; 50 mg/kg) and placed in a stereotaxic apparatus. The scalp was incised and retracted, and small burr holes were drilled in the skull for bilateral placement of guide cannulae (26 gauge; 6 mm in length; Plastics One, Virginia) at the following coordinates: 0.7 mm anterior to bregma and 3.6 mm lateral to midline, and 5 mm below skull surface. Dental acrylic and machine screws were used to fix the cannulae to the skull. After surgery, dummy cannulae (33 gauge; 6.5 mm in length; Plastics One) were inserted into the guides.

At the end of the experiment, the rats were sacrificed using a lethal barbiturate overdose (sodium pentobarbital, 100 mg/kg) and perfused transcardially with 0.9% saline followed by 10% formaldehyde solution. The brains were stored in a 25% sucrose-formalin solution for at least 3 days before 50  $\mu$ m coronal sections were cut, and stained with thionin for histological examination.

### 1.3. Lever-press training

Five days after surgery, rats were placed on a food deprivation schedule, receiving 10–12 g of their maintenance diet daily to reduce

their weight to 80–85% of their free-feeding weight. Once training began, they were fed each day after the training sessions, and had free access to water while in their home cages. Throughout this period, the dummy cannulae were removed and replaced every other day.

Ten days after surgery, rats were given two 30 min magazine training sessions in which the reinforcer (0.1 ml of 20% sucrose solution) was delivered on a random time 60 s schedule (once a minute on average) with the levers removed. Rats were left in the instrumental chamber for 1 h between these two sessions. This training was designed to acquaint the animals with the location of the magazine where food is delivered.

The lever-press training began the next day. Each training session began with the illumination of the house light and insertion of a single lever, and ended with the retraction of the levers and turning off of the house light. The house light was located on the other side of the food magazine, and close to the ceiling of the chamber; the lever was located on the same side and just to the left of the food magazine. The rats were first trained under a fixed interval 20 s (FI-20 s) schedule, in which a reinforcer became available every 20 s, and was delivered as soon as the rat pressed the lever. This training ended as soon as 100 reinforcers were earned or after 90 min had expired. As soon as the rats were able to earn 100 reinforcers in a single session (which took five sessions of training), they were switched to a random interval-30 s schedule (RI-30 s) for one session. Under this schedule, a reinforcer became available every 30 s on average. Finally, they received four daily sessions of training under an RI-60 s schedule. This particular combination of schedules of reinforcement was used because our previous work has shown that such a training regimen is sufficient to generate habitual lever pressing that is insensitive to devaluation of the outcome [44].

#### 1.4. Muscimol infusion and omission training

Immediately before the omission session, 14 rats received bilateral infusions of muscimol into the DLS, 18 rats received vehicle infusions. The dummy cannulae were removed and injection cannulae (26 gauge; Plastics One, Virginia) were lowered into the guide cannulae, with an extension of 0.5 mm. The injecting cannulae were connected by polyethylene tubing to 10  $\mu$ l Hamilton syringes mounted on an infusion pump (Harvard). Muscimol (Sigma, MO, USA; 1  $\mu$ g/ $\mu$ l dissolved in 0.9% phosphate-buffered saline) was delivered at a rate of 0.25  $\mu$ l/min for 2 min, with a total volume of 0.5  $\mu$ l per side. This infusion protocol was selected based on measurements of muscimol diffusion and 2-deoxyglucose activity [33]. The same volume of phosphate-buffered saline was used as the vehicle. One minute after infusion, the dummy cannulae were replaced.

Half of the rats in each infusion group were assigned to the omission group, and the other half to the yoked control group. For the omission group, sucrose was delivered every 20 s without lever pressing. A timer automatically counted to 20 s, at which point the reinforcer was delivered, but each press would reset the timer to 0. For the yoked controls, each rat was assigned to a rat in the omission group, and received exactly the same number of sucrose deliveries at exactly the same time as the rat under omission contingency. Thus for this group, the conditions are identical to those of the omission group except that their responses were not scheduled to prevent sucrose delivery. The omission session lasted 30 min, after which the rats were returned to their home cages.

The next day, approximately 24 h after the omission session, all rats were returned to the instrumental chambers for a 10 min extinction session, in which the lever was extended, but no reinforcer was delivered.

## 2. Results

### 2.1. Placement of the implanted cannulae

Fig. 1 provides a schematic representation of the cannulae placement in the striatum. As shown in this figure, the can-

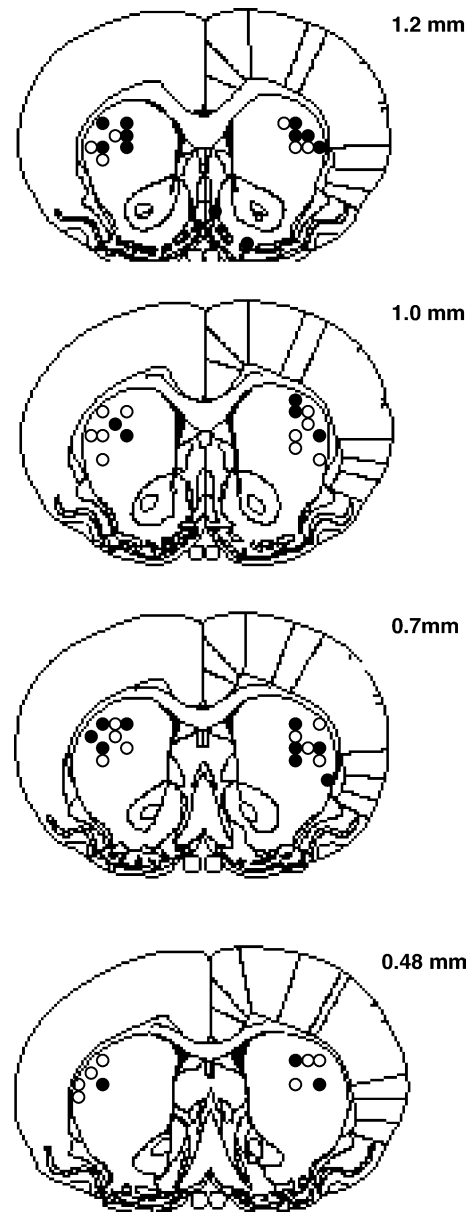


Fig. 1. The locations of cannulae tips. Rats in the vehicle group are represented by open circles and rats in the muscimol group are represented by filled circles; and some of the circles represent multiple cannulae tips. Numbers beside each plate correspond to the distances from bregma in millimeter (plates adapted from [36]).

nulae were primarily placed in the dorsolateral region of the striatum.

### 2.2. Omission session behavior

The mean response rates on the last day of lever-press training are presented as the baseline in Fig. 2 (first data point in the graphs). Using treatment (muscimol and vehicle) and contingency (omission and yoked) as factors, a two-way ANOVA was conducted. No interaction between treatment and contingency was found ( $F < 1$ ). There was no main effect of contingency ( $F_{1,28} = 1.2$ ,  $p > 0.05$ ). Neither the rats receiving muscimol nor the rats receiving vehicle showed significant sensitivity to the omission contingency during this session. That is, for each treatment there was no difference between rats receiving the omission contingency and their yoked controls. There was, however, a main effect of treatment: the total number of lever-presses was reduced in rats (both omission and yoked) that received muscimol before the session, showing that DLS inactivation reduced lever pressing generally ( $F_{1,28} = 12.26$ ,  $p < 0.01$ ), for both animals on the omission schedule and their yoked controls. This pattern is not true of head entries into the food magazine—on this measure the two groups were similar, with no main effect of treatment or of contingency ( $F < 1$ ), or any interaction between these factors ( $F_{1,28} = 1.59$ ,  $p > 0.2$ ).

The reduced responding seen in rats that received muscimol was not due to their inability to press the lever, because they were able to press just as quickly as the other two groups, as shown by the highest response rates per minute across the omission training session (Fig. 2C). A two-way ANOVA revealed no main effect of treatment, of contingency, nor any interaction between these factors ( $F < 1$ ).

We also performed an analysis on exactly when during the 30 min session the highest-responding minute occurred for each group, i.e. which minute had the highest response rate (mean values  $\pm$  S.E.M.: muscimol, omission =  $4.14 \pm 1.39$ ; muscimol, yoked =  $7.14 \pm 1.92$ ; vehicle, omission =  $6.44 \pm 2.17$ ; vehicle, yoked =  $9.56 \pm 2.73$ ). There is no main effect either of treatment or of contingency, nor any interaction between these two factors on this measure (largest  $F = 1.85$ ).

### 2.3. Extinction test

The critical data that reveal what the animals learned during the omission session were collected in a 10 min extinction test on the next day, without any drug infusion. The results from this test are shown in Fig. 3. A two-way ANOVA conducted on the total number of responses during this session revealed no main effect of treatment ( $F < 1$ ), and a nearly significant main effect of contingency ( $F_{1,28} = 3.95$ ,  $p = 0.057$ ). There was also a significant interaction between these two factors ( $F_{1,28} = 6.72$ ,  $p < 0.05$ ). Simple main effects

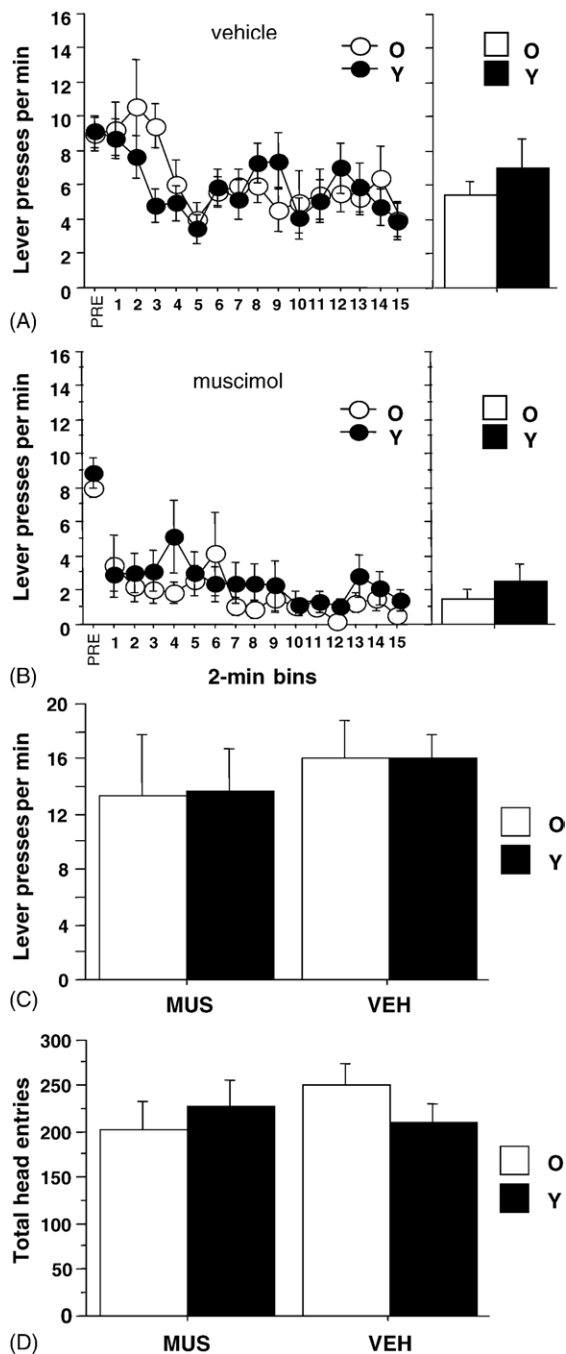


Fig. 2. The number of lever-presses and head entries for each group during the 30 min omission session. (A) Vehicle; (B) muscimol; (C) highest rate of lever pressing per minute reached by all groups; (D) total number of head entries during the omission session. PRE, baseline level of responding at the end of instrumental training; O, omission; Y, yoked; MUS, muscimol group; VEH, vehicle group.

analysis conducted on this interaction revealed that only the rats receiving muscimol showed sensitivity to omission: the lever-presses in the omission group was significantly lower than those of their yoked controls ( $F_{1,28} = 11.96$ ,  $p < 0.01$ ).

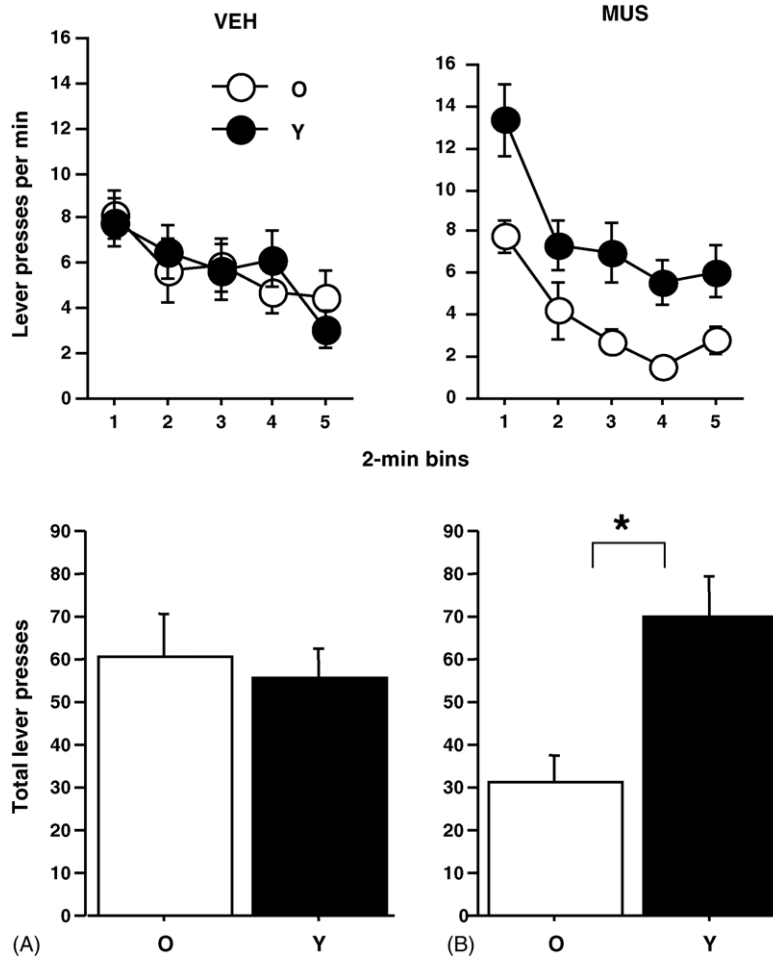


Fig. 3. The number of lever-presses for each group during the 10 min extinction test. (A) Vehicle; (B) muscimol. O, omission; Y, yoked; MUS, muscimol group; VEH, vehicle group.

### 3. Discussion

This study consisted of three phases: (1) lever-press training; (2) omission session after muscimol or vehicle infusion; (3) extinction test without drug infusion. Such a design aimed to assess whether DLS inactivation would affect learning during the omission session, i.e. learning about the complete reversal in instrumental contingency. As we predicted on the basis of previous work, rats given vehicle infusions were insensitive to the imposition of the omission contingency and failed to learn to withhold responding during this single short session of training in order to earn rewards. This loss of instrumental control is characteristic of habitual actions mediated by an S–R associative structure—not surprisingly, as the interval schedules of reinforcement used in the initial training phase were designed to generate habitual behavior [17,18,44]. In fact, the present study provides the first direct evidence that training with a single action–outcome pairing under interval schedules can result in insensitivity to omission contingency relative to yoked controls.

In contrast, rats that received muscimol infusions into the DLS showed enhanced learning of the omission

contingency—they learned to withhold responding relative to their yoked controls. Thus, it appears that inactivation of the DLS during omission resulted in increased sensitivity to this contingency. As the DLS is thought to be a crucial component of the neural circuit mediating habitual behavior [7,32,34], the present findings point to its important role in maintaining habitual behavior during omission training and preventing learning of the complete reversal in action–outcome contingency. The present study thus provides additional evidence for the existence of two independent neural systems for the control of voluntary behavior [14], by showing that reversible disruption of the habit system enhances learning mediated by the goal-directed system—namely learning of the negative contingency between lever pressing and sucrose during the omission session, as revealed on the subsequent extinction test.

The reduction in lever pressing caused by muscimol infusion may explain why these rats failed to display sensitivity to omission in the session in which they were under the influence of the drug; the lack of any difference between rats under omission and their yoked controls in this session likely reflects a ‘floor effect’; i.e. the response rates were too low

to reveal any difference. Although DLS inactivation caused a general reduction in the number of lever-presses in rats in both the omission group and in their yoked counterparts, this reduction in responding cannot be attributed to a simple motor deficit. First, the number of head entries in the magazine was not reduced in the muscimol group (Fig. 2D), indicating that the reduction in responding was restricted to lever pressing. More importantly, a detailed analysis of the lever pressing data showed that, under the influence of muscimol, the rats were clearly able to respond just as quickly as the other two groups (Fig. 2C). Together these observations rule out the possibility that muscimol infused into the DLS at the dose used in the present study impaired the rats' ability to perform the lever-press action.

It is possible, however, that the influence of muscimol on instrumental performance allowed the rats to adjust to the imposition of omission through a subtler alteration in motor control. For example, the dorsal striatum is known to be critical for action sequencing [9], and it is possible that muscimol produced a selective change in the sequencing of the lever-press action that reduced the tendency to maintain a high rate of responding over the course of the session. This reduction in response sequencing may then have allowed the rats the opportunity to utilize alternative response strategies; indeed, it is probably through variations in motor control of this kind that habitual and goal-directed strategies compete for influence over instrumental performance. Whatever its basis, however, the lower rates of lever pressing during the omission session could not have solely been responsible for the enhanced sensitivity to omission shown by the muscimol-infused animals, because their yoked controls, exposed to an equal number of non-contingent rewards, responded similarly in this session, yet their performance on the extinction test did not differ from vehicle-infused groups (clearly dissociating learning from performance).

Based on previous research, another explanation for better acquisition of omission in the muscimol-infused rats is response competition: i.e. the performance of lever pressing could have been reduced in the muscimol infused omission group on test if, during the training phase, they acquired a response that competed with the lever-press response on test. The reduced responding relative to yoked controls, shown in the extinction test the next day by the muscimol group, could then be attributed to differential reinforcement of that other behavior. There are few candidate responses of this kind, but one that has been identified in previous research is the approach response to the food magazine during the omission session [1]. This account predicts that rats under the influence of muscimol, with more experience of free rewards due to their low rates of lever pressing, would acquire a stronger tendency to enter the magazine than rats that received vehicle infusions. Although plausible, this account is not supported by our data (see Fig. 2D), which show comparable levels of magazine entry in these two groups during the test. It is not clear, therefore, how differences in responding during omission training could explain differences in performance on test.

Abnormal cortico-striatal functioning has been implicated in obsessive-compulsive disorder and addiction [37]. The striking insensitivity to omission displayed by rats after extended training under interval schedules appears to be characteristic of such compulsive behavior. A pathological potentiation of the habit circuit or an impairment in inhibitory control is often hypothesized to be responsible for these disorders [19,21,23,37]. According to Pitman [37], for example, the genesis of compulsive behavior in humans can often be traced to a particular reinforcement history of the behavior, which becomes resistant to extinction and divorced from consummatory activities. These characteristics are ascribed to enhanced dopaminergic transmission in the cortico-striatal circuit [37]. In recent years, we have learned more about the habit system in question. We now know that the DLS plays a crucial role in habitual behaviors that persist despite outcome devaluation [44], and that dopaminergic innervation of this striatal region is probably needed for such habit formation [20,28]. These observations are broadly in accord with Pitman's original speculations. However, while traditionally the habit system is thought to be inhibited by a more flexible neural system consisting mainly of the hippocampus and related structures, recent work has shown that the alternative system of goal-directed actions that acquires action–outcome contingencies is the associative cortico-basal ganglia system, including the dorsomedial striatum, which incidentally also receives projections from the hippocampus [43,45,46]. As a consequence, the medial prefrontal cortex, dorsomedial striatum, and downstream structures now appear to constitute the primary neural system responsible for flexible, goal-directed actions, though the contribution of the hippocampus remains unclear. Whether this system is a source of inhibitory control over the habit system has yet to be experimentally tested. Given the present results, however, the converse is plausible—i.e. the habit system may limit the learning of changing action–outcome contingencies, and disrupting the habit system appears to permit such learning.

At any rate, one implication of our results that deserves emphasis is that different cortico-basal ganglia networks could interact with each other, in accord with recent anatomical work that also has focused on connections between circuits rather than the more strictly parallel and segregated circuitry proposed by traditional models of the basal ganglia [2,26,27,29–31]. Such interaction is clearly of major functional significance to our understanding of how goal-directed actions could be transformed into habits, how behavior under instrumental control could become compulsive. Anatomically, interaction could occur at each component of the network—cortical, striatal, pallidal, as well as downstream structures [25–27,29–31,41]. Future studies that directly test these possibilities will undoubtedly shed light on this critical issue.

Finally, a persistent problem in the experimental study of compulsive behaviors is the lack of a well-established assay that captures the main characteristics of compulsion. In our opinion, the omission procedure provides such an assay in

assessing the instrumental control of behavior in animal models of compulsive disorders and addiction. Furthermore, as our results suggest, specific pharmacological manipulation of the habit circuit may be a promising research strategy in elucidating the detailed mechanisms underlying the development of compulsive behavior.

## Acknowledgements

This research was supported by an NSF graduate fellowship to HHY, NSF grant 9985417 to BJK and NIMH grant MH 56446 to BWB.

## References

- [1] Adams S, Kesner RP, Ragozzino ME. Role of the medial and lateral caudate-putamen in mediating an auditory conditional response association. *Neurobiol Learn Mem* 2001;76:106–16.
- [2] Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* 1990;13:266–71.
- [3] Brown LL, Smith DM, Goldbloom LM. Organizing principles of cortical integration in the rat neostriatum: corticostriate map of the body surface is an ordered lattice of curved laminae and radial points. *J Comp Neurol* 1998;392:468–88.
- [4] Brown VJ, Desimone R, Mishkin M. Responses of cells in the tail of the caudate nucleus during visual discrimination learning. *J Neurophysiol* 1995;74:1083–94.
- [5] Brown VJ, Robbins TW. Elementary processes of response selection mediated by distinct regions of the striatum. *J Neurosci* 1989;9:3760–5.
- [6] Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci Biobehav Rev* 2002;26:321–52.
- [7] Carelli RM, Wolske M, West MO. Loss of lever press-related firing of rat striatal forelimb neurons after repeated sessions in a lever pressing task. *J Neurosci* 1997;17:1804–14.
- [8] Colwill RM, Rescorla RA. Associative structures in instrumental learning. In: Bower G, editor. *The psychology of learning and motivation*, vol. 20. New York: Academic Press; 1986. p. 55–104.
- [9] Cromwell HC, Berridge KC. Implementation of action sequences by a neostriatal site: a lesion mapping study of grooming syntax. *J Neurosci* 1996;16:3444–58.
- [10] Davis J, Bitterman ME. Differential reinforcement of other behavior (DRO): a yoked-control comparison. *J Exp Anal Behav* 1971;15:237–41.
- [11] Dawson GR, Dickinson A. Performance on ratio and interval schedules with matched reinforcement rates. *Quart J Exp Psychol B* 1990;42:225–39.
- [12] Devan BD, McDonald RJ, White NM. Effects of medial and lateral caudate-putamen lesions on place- and cue-guided behaviors in the water maze: relation to thigmotaxis. *Behav Brain Res* 1999;100:5–14.
- [13] Devan BD, White NM. Parallel information processing in the dorsal striatum: relation to hippocampal function. *J Neurosci* 1999;19:2789–98.
- [14] Dickinson A, Balleine B. Actions and responses: the dual psychology of behaviour. In: Eilan N, McCarthy RA, editors. *Spatial representation: problems in philosophy and psychology*. Malden, MA, USA: Blackwell Publishers Inc.; 1993. p. 277–93.
- [15] Dickinson A, Campos J, Varga ZI, Balleine B. Bidirectional instrumental conditioning. *Quart J Exp Psychol: Comp Physiol Psychol* 1996;49:289–306.
- [16] Dickinson A, Charnock DJ. Contingency effects with maintained instrumental reinforcement. *Quart J Exp Psychol: Comp Physiol Psychol* 1985;37:397–416.
- [17] Dickinson A, Nicholas DJ, Adams CD. The effect of the instrumental training contingency on susceptibility to reinforcer devaluation. *Quart J Exp Psychol: Comp Physiol Psychol* 1983;35:35–51.
- [18] Dickinson A, Squire S, Varga Z, Smith JW. Omission learning after instrumental pretraining. *Quart J Exp Psychol* 1998;51:271–86.
- [19] Everitt BJ, Wolf ME. Psychomotor stimulant addiction: a neural systems perspective. *J Neurosci* 2002;22:3312–20.
- [20] Faure A, Haberland U, Conde F, El Massioui N. Lesion to the nigrostriatal dopamine system disrupts stimulus–response habit formation. *J Neurosci* 2005;25:2771–80.
- [21] Gerdeman GL, Partridge JG, Lupica CR, Lovinger DM. It could be habit forming: drugs of abuse and striatal synaptic plasticity. *Trends Neurosci* 2003;26:184–92.
- [22] Graybiel AM. The basal ganglia and chunking of action repertoires. *Neurobiol Learn Mem* 1998;70:119–36.
- [23] Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron* 2000;28:343–7.
- [24] Grillner S, Hellgren J, Menard A, Saitoh K, Wikstrom MA. Mechanisms for selection of basic motor programs—roles for the striatum and pallidum. *Trends Neurosci* 2005.
- [25] Haber S, McFarland NR. The place of the thalamus in frontal cortical-basal ganglia circuits. *Neuroscientist* 2001;7:315–24.
- [26] Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat* 2003;26:317–30.
- [27] Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 2000;20:2369–82.
- [28] Ito R, Dalley JW, Robbins TW, Everitt BJ. Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *J Neurosci* 2002;22:6247–53.
- [29] Joel D, Weiner I. The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. *Neuroscience* 1994;63:363–79.
- [30] Joel D, Weiner I. The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. *Brain Res Brain Res Rev* 1997;23:62–78.
- [31] Joel D, Weiner I. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 2000;96:451–74.
- [32] Jog MS, Kubota Y, Connolly CI, Hillegaart V, Graybiel AM. Building neural representations of habits. *Science* 1999;286:1745–9.
- [33] Martin JH. Autoradiographic estimation of the extent of reversible inactivation produced by microinjection of lidocaine and muscimol in the rat. *Neurosci Lett* 1991;127:160–4.
- [34] Packard MG, Knowlton BJ. Learning and memory functions of the Basal Ganglia. *Annu Rev Neurosci* 2002;25:563–93.
- [35] Packard MG, McGaugh JL. Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiol Learn Mem* 1996;65:65–72.
- [36] Paxinos G, Watson C. *The rat brain in stereotaxic coordinates*. San Diego: Academic Press; 1998.
- [37] Pitman RK. Animal models of compulsive behavior. *Biol Psychiatry* 1989;26:189–98.
- [38] Ragozzino ME. Acetylcholine actions in the dorsomedial striatum support the flexible shifting of response patterns. *Neurobiol Learn Mem* 2003;80:257–67.
- [39] Ragozzino ME, Jih J, Tzavos A. Involvement of the dorsomedial striatum in behavioral flexibility: role of muscarinic cholinergic receptors. *Brain Res* 2002;953:205–14.
- [40] Tai CT, Clark AJ, Feldon J, Rawlins JN. Electrolytic lesions of the nucleus accumbens in rats which abolish the PREE enhance the locomotor response to amphetamine. *Exp Brain Res* 1991;86:333–40.

- [41] Tunstall MJ, Oorschot DE, Kean A, Wickens JR. Inhibitory interactions between spiny projection neurons in the rat striatum. *J Neurophysiol* 2002;88:1263–9.
- [42] Whishaw IQ, Mittleman G, Bunch ST, Dunnett SB. Impairments in the acquisition, retention and selection of spatial navigation strategies after medial caudate-putamen lesions in rats. *Behav Brain Res* 1987;24:125–38.
- [43] Yin HH, Knowlton BJ. Contributions of striatal subregions to place and response learning. *Learn Mem* 2004;11:459–63.
- [44] Yin HH, Knowlton BJ, Balleine BW. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur J Neurosci* 2004;19:181–9.
- [45] Yin HH, Knowlton BJ, Balleine BW. Blockade of NMDA receptors in the dorsomedial striatum prevents action–outcome learning in instrumental conditioning. *Eur J Neurosci* 2005;22:505–12.
- [46] Yin HH, Ostlund SB, Knowlton BJ, Balleine BW. The role of the dorsomedial striatum in instrumental conditioning. *Eur J Neurosci* 2005;22:513–23.