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Discriminated Escape Learning and Response to Electric Shock after 6-Hydroxydopamine Lesions of the Nigro-Neostriatal Dopaminergic Projection

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PRICE, M. T. C. AND H. C. FIBIGER. *Discriminated escape learning and response to electric shock after 6-hydroxydopamine lesions of the nigro-neostriatal dopaminergic projection.* PHARMAC. BIOCHEM. BEHAV. 3(2) 285–290, 1975. – In an earlier report it was observed that bilateral stereotaxic injections of 6-hydroxydopamine (6-OHDA) into the zona compacta of the substantia nigra produced deficits in the acquisition of a conditioned avoidance response [8]. The present experiments were designed to determine if either a generalized learning impairment or a decreased sensitivity to foot shock might be the basis for the avoidance deficit. It was found that rats subjected to bilateral 6-OHDA lesions of the substantia nigra learned a light discrimination shock escape habit in as few trials as unoperated controls. This observation indicates that the integrity of the dopaminergic nigro-neostriatal system is not essential for the formation of learned associations between sensory cues and motor responses. In a second experiment it was observed that neither the shock-induced flinch nor the jump threshold was elevated after nigral lesions, suggesting that these lesions do not decrease the aversive motivational properties of foot shock. In view of these findings, the nature of the avoidance deficit produced by substantia nigra lesions is discussed with reference to the possibility that they selectively block the initiation of voluntary motor responses. According to this hypothesis, the failure of these lesions to disrupt escape responding may be due to the fact that the unconditioned stimulus generates reflexive motor responses (flinch, jump, etc.) which are sufficient to begin the motor sequences that cannot be initiated voluntarily in response to the conditioned stimulus.

Nigro-neostriatal dopamine neurons 6-Hydroxydopamine Learning Instrumental responding
Catecholamines

IT has recently been demonstrated that bilateral lesions of the nigro-neostriatal dopaminergic projection induced by stereotaxic injections of 6-hydroxydopamine (6-OHDA) into the zona compacta of the substantia nigra results in a severe impairment in the acquisition of a conditioned avoidance response (CAR) and of an approach response for food reinforcement [8]. At least three factors should be considered in further investigations of this behavioural deficit. These include impaired motor function, decreased learning ability and motivational changes. With regard to the first possibility, the fact that during CAR training the lesioned animals are not impaired on the escape response suggests that the failure to acquire the avoidance response is not due to a severe and non-specific motor deficit [8]. The fact that animals which are overtrained on the avoidance response prior to receiving bilateral substantia nigra lesions are not subsequently impaired in avoidance responding also suggests that it is unlikely that these lesions produce general and non-specific motor deficits [8,24].

In the experiments reported here, explanations for the CAR deficit in terms of learning and motivation were examined. In Experiment 1, it was hypothesized that the integrity of the nigro-neostriatal system may be essential to the formation of new associations between sensory cues and motor responses; that is, that failure to acquire the avoidance response was due to a failure to learn the significance of the conditioned stimulus. In Experiment 2, the hypothesis tested was that the lesions effected a motivational change arising from an increased threshold for aversiveness of shock.

EXPERIMENT 1

As was referred to above, rats with bilateral 6-OHDA lesions of the substantia nigra will escape from shock even

though they do not avoid it. This being the case, the use of a shock-escape discrimination task could permit an evaluation of the association-type learning deficit. If the CAR deficit is due to an impaired ability to learn the significance of sensory cues then the acquisition of a discriminated escape response should also be disrupted by these lesions. If, on the other hand, the ability to use sensory cues is not the basis for the CAR deficit, then animals with substantia nigra lesions would be expected to show normal acquisition of this habit.

METHOD

Animals

Twenty-three naive male Wistar rats were tested. They weighed 300–320 g at the beginning of the experiment. Animals were maintained individually in stainless steel cages with water and Purina Rat Chow available ad lib. Throughout the experiment, colony lighting was on from 8:00 a.m. to 8:00 p.m.

Surgery. Precisely the same stereotaxic coordinates, doses of 6-OHDA, and postoperative care were used as in the earlier CAR experiments [8]. Unoperated animals served as controls. Sixteen animals were anaesthetized with Nembutal (50 mg/kg) and prepared for surgery in a Kopf stereotaxic instrument. Nine animals were injected with 8 μg of 6-hydroxydopamine hydrobromide (dosage expressed as the free base) in a volume of 2 μl bilaterally into the substantia nigra. The 6-OHDA was dissolved in a solution of 0.15 M NaCl and 0.2 mg/ml ascorbic acid and was injected at a rate of 1 μl/min. The injection coordinates according to König and Klippel [16] were A + 3.2 mm; L + 2.1 mm; and DV − 2.1 mm. To control for possible damage to the ventral noradrenergic projection [8] an additional group of 7 animals were injected bilaterally into this bundle. Injections were made caudal to the substantia nigra so as not to damage the nigro-neostriatal projection. The coordinates according to König and Klippel [16] were A + 1.0 mm; L + 1.3 mm; and DV − 2.1 mm.

Convalescence. As has been reported previously [9] animals receiving 6-OHDA lesions to the substantia nigra became aphagic and adipsic to different degrees and for varying periods of time. Severely aphagic and adipsic animals were intubated twice daily with 15 cc of artificial mother's milk (Lactol, 25% by volume, 75% tap water). Other animals that ingested insufficient quantities of water and food to maintain their weights were intubated once daily. Since animals that recovered self-feeding showed a post-operative change in food preferences, they were offered a choice of two alternative diets. These diets were canned dog food and/or a mixture of margarine, mash and sugar in the proportion 6:10:1. The five animals that did not recover sufficiently to maintain their weights continued to be tube fed throughout the experiments. Despite the attention given to postoperative care 2 animals did not survive surgery.

Apparatus

Testing was carried out in a Y-maze constructed of plywood and lucite. The arms of the maze measured 13.5 × 6 × 5 in. A 40 W lamp was located behind a lucite panel at the end of each arm. The floor consisted of 3/32 in dia. grids, spaced 3/8 in. apart. An a.c. shock scrambler delivered 1.3 mA intermittent shock, 1 sec in duration at 3 sec intervals to the grid floor of the maze.

Procedure

Light discrimination learning. Three groups of animals, unoperated controls (n = 7) those receiving lesions to the substantia nigra (n = 7) or the ventral bundle (n = 7) were trained on a light discrimination shock escape task. Nigral-lesioned animals that were self-feeding, and ventral bundle and control animals were handled for 4 min per day on the 4 days preceeding training in order to partially control for handling of the tube fed nigral-lesioned animals. Testing was carried out approximately 6 weeks after surgery.

Training began by placing an animal into the one unlighted shock-free alley of the maze. After a 1 min interval this alley was lighted, the grids were electrified and one of the previously lighted alleys became the unlighted shock-free alley. The animal had to find its way to the unlighted alley to attain respite from shock, and remain in this alley for 60 consecutive secs to complete a trial. Training continued until the animal had correctly chosen the unlighted shock-free alley on 9 consecutive trials.

Biochemistry. Upon completion of the behavioral experiments the animals were killed by cervical fracture and the striatum and hypothalamus were dissected out from each brain. Striatal dopamine and hypothalamic norepinephrine were measured by the method of McGeer and McGeer [18].

Histology. The caudal portion of the brains of all experimental animals were fixed in buffered Formalin prior to embedding in paraffin wax. Serial sections (20 μ) were taken through the substantia nigra and every fourth section mounted, stained with luxol fast blue and counterstained with thionin.

RESULTS AND DISCUSSION

Discrimination Learning

The number of trials taken to reach the learning criterion for the three groups is presented in Table 1. The nigral-lesioned and control groups did not differ significantly in the number of trials taken to reach the learning criterion (t = 0.6, n.s.). It appears, then, that lesions to the substantia nigra do not impair the ability to associate a visual cue with a motor response. Since the performance of the ventral bundle group was significantly more variable than that of the control group ($F = 10.9$, $p<0.02$) a nonparametric test, the Mann-Whitney U, was used. The control and ventral bundle groups did not differ significantly according to this test (U = 13, n.s.). In general, the rats in this group appeared to be extremely excited and agitated in response to the foot shock and in some cases this reached the point where it obviously adversely affected the performance. However, other animals in this group reached criterion in as few trials as controls.

One animal that had received lesions to the ventral bundle was removed from the maze after completing 40 trials but before the learning criterion was reached. This animal persisted in jumping out of the correct alley during the 60 sec intertrial interval. The number of intertrial crossings appeared to increase with increasing trials.

Biochemistry and Histology

The biochemical results are presented in Table 2. The groups differed on both striatal dopamine ($p<0.01$) and hypothalamic norepinephrine ($p<0.01$) levels. Striatal

TABLE 1

THE EFFECT OF 6-OHDA LESIONS OF THE SUBSTANTIA NIGRA OR VENTRAL NA BUNDLE ON THE NUMBER OF TRIALS REQUIRED TO LEARN A DISCRIMINATED SHOCK ESCAPE HABIT

Controls	6-OHDA Nigral	6-OHDA Ventral Bundle
21.0 ± 3.5	25.4 ± 6.0	40.2 ± 11.3

Data represent means (± S.E.M.) of 7 animals in each group. There was not a statistically significant difference between the groups.

TABLE 2

EFFECT OF 6-OHDA LESIONS OF THE SUBSTANTIA NIGRA AND THE VENTRAL NA BUNDLE ON NEOSTRIATAL DOPAMINE AND HYPOTHALAMIC NORADRENALINE LEVELS

	Striatal Dopamine (μg/gm)	% Control	Hypothalamic Noradrenaline (μg/gm)	% Control
Controls	12.60 ± 0.89	100	1.80 ± 0.19	100
6-OHDA – SN	0.22 ± 0.09*	1.7	0.50 ± 0.08*	27.8
6-OHDA – Ventral bundle	11.00 ± 1.64	87.3	0.27 ± 0.11*	15.0

Data represent means (± S.E.M.) of 10–11 animals in each group. Dopamine and noradrenaline were measured according to McGeer and McGeer (1962).

*Significantly different from controls, $p<0.001$

dopamine of the nigral animals was reduced by about 98 percent. Post hoc tests showed that levels for this group were significantly less than those of both the ventral bundle and control groups ($p<0.01$). Dopamine of the ventral bundle animals was reduced by about 13 percent but this was not a statistically significant effect. Hypothalamic norepinephrine of the ventral bundle animals was reduced by 85 percent, and for the nigral animals the reduction was about 72 percent. Ventral bundle levels were lower than those of both the control ($p<0.01$) and the nigral ($p<0.01$) animals. Norepinephrine levels of nigrals were, as well, lower than control levels ($p<0.01$).

Histological analysis revealed that the damage produced by 6–OHDA was confined primarily to the zona compacta of the substantia nigra. Considerable gliosis was observed in this region. Cells in the zona reticulata appeared normal. Small amounts of gliosis were observed in cell group A10 near the interpeduncular nucleus. In some animals a few necrotic cells were observed in the ventral part of the red nucleus, but the vast majority of cells in this region appeared normal.

Since animals with lesions to the substantia nigra did learn the discrimination, it appears that destruction of this system does not impair, at least under the conditions of the present experiment, the ability to associate a sensory cue with a motor response. The results of a similar unpublished experiment referred to by Ungerstedt [23] that nigral-lesioned rats could learn a light discrimination in a water Y-maze support this conclusion. Regarding the previously reported failure by nigral lesioned animals to acquire a CAR [8], these findings appear to make less tenable the hypothesis that the CAR deficit is the result of a generalized learning impairment.

EXPERIMENT 2

In this experiment the hypothesis that lesions of the nigro-neostriatal system produce a decrease in sensitivity to foot shock was evaluated.

METHOD

Animals

Included in Experiment 2 were all control animals (n = 10), and those receiving nigral lesions (n = 10) or ventral bundle lesions (n = 11) that were tested in Experiment 1 or used in a pilot study for that experiment. The interval between Experiment 1 and 2 was 4 weeks.

Apparatus

Animals were tested in a Plexiglas chamber measuring 10 X 9.5 X 17 in. A shock generator delivered shock to the floor of the chamber which consisted of 1/10 in. dia. grids, spaced 0.5 in. apart.

Procedure

The response to shock was measured by a modification of the Evans [6] flinch-jump method. Rats were given 10 series of 200 msec shocks in alternating increasing and decreasing intensities. A descending series was terminated after an animal had not flinched on 3 consecutive descending intensities or when the lowest intensity utilized was reached. An ascending series was terminated after 3 consecutive jumps were observed. A new series began with the last intensity used in a previous series. This modification of Evans' [6] procedure was adopted after preliminary testing indicated that animals with lesions to the ventral bundle became very agitated on receiving a considerable number of shocks after the jump threshold had been reached.

Immediately prior to testing, an animal's feet were wiped with electrode paste. Testing began 2 min after placement into the test chamber. The shock intensities used were: 0.05, 0.1, 0.125, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, and 3.4 mA. Shocks were presented at 10 sec intervals, and series were separated by 30 sec intervals.

Data Analysis

At the end of each shock an animal's behavior was rated as either (1) no response, (2) flinch (rear paws do not leave the grids), or (3) jump (both rear paws leave the grids or running occurs). Flinch and jump thresholds were defined as the lowest shock intensity at which the respective responses were observed on at least 5 of the 10 trials.

RESULTS AND DISCUSSION

The means and standard errors of the flinch and jump thresholds for the three groups are presented in Table 3. One-way analysis of variance showed that only the flinch thresholds differed significantly ($p<0.01$). Further analysis showed that the thresholds of the animals receiving lesions to the substantia nigra were significantly lower than both the ventral bundle group and control animals ($p<0.01$). Although the jump thresholds of the ventral bundle animals appeared to be lower than those of the other groups, when tested by analysis of variance, the F value just failed to reach statistical significance. However, there was a significant reduction in the jump threshold of the ventral bundle group as determined by Student's t test ($p<0.05$). It should be noted that as was the case in the discriminated escape task, the response of the rats with ventral bundle lesions to foot shock was qualitatively different from the control group. The emotional response of these animals to foot shock was very much exaggerated and they appeared to be very agitated during this procedure. These hyperreactive animals were very vocal and often would attack the grids. In addition, these animals would often jump at what appeared to be the detection threshold.

The findings that neither the flinch nor the jump thresholds were elevated in the nigral-lesioned animals does not support the hypothesis that the CAR deficit observed in similarly treated animals reflects a decreased motivation to perform the avoidance response. It remains possible of course that the nigral lesions produce a perceptual sensory deficit that cannot be detected by the flinch-jump test and that may be significant in the CAR deficit. Nevertheless, the flinch-jump results suggest that nigral lesions do not produce a state of analgesia which serve to decrease the motivational properties of foot shock. In fact, nigral-lesioned rats had a significantly lower flinch threshold than did the controls. The significance of this observation is not immediately apparent but it may simply reflect the fact that the nigral-lesioned animals weighed significantly less than the other groups (controls 439 ± 20 g; nigral-lesioned 292 ± 9 g; ventral-bundle lesioned 473 ± 19 g) and Gibbs *et al.* [11] have shown that flinch and jump thresholds vary as a function of body weight.

GENERAL DISCUSSION

The present experiments demonstrate that animals with bilateral 6-OHDA lesions of the substantia nigra do not have a generalized learning deficit and do not appear to be less sensitive to foot shock. These findings do not therefore support the hypothesis that the avoidance deficit observed in rats with bilateral nigral lesions reflects either failure to learn the significance of the CS, or decreased motivation arising from increased shock aversion thresholds.

In order to gain further insight into the nature of the CAR deficit produced by substantia nigra lesions it may be useful to compare the effects of these lesions with the disruption of avoidance responding produced by neuro-

TABLE 3

THE EFFECT OF 6-OHDA LESIONS OF THE SUBSTANTIA NIGRA OR VENTRAL NA BUNDLE ON FLINCH AND JUMP THRESHOLDS (IN MILLIAMPERES)

	Controls	6-OHDA Nigral	6-OHDA Ventral Bundle
Flinch	0.42 ± 0.04	0.23 ± 0.02*	0.47 ± 0.05
Jump	0.94 ± 0.07	0.88 ± 0.08	0.75 ± 0.05

Data represent means (± S.E.M.) of 10–11 animals in each group.
*Significantly different from controls, $p<0.01$

leptic drugs. At a theoretical level it might be predicted that these two treatments would produce similar effects on CAR because in one case the dopaminergic input to the neostriatum is lesioned, while in the other the dopamine receptors are blocked pharmacologically [2]. In fact, the effects of these two treatments on CAR are remarkably similar. First, both procedures selectively disrupt avoidance but not escape responses [4, 8, 12]. Secondly, the disruption produced by either treatment can be ameliorated by a number of antiParkinsonian drugs [5, 10, 24]. Thirdly, prior overtraining of the avoidance response markedly reduces the disruption of CAR produced by both of these procedures [8, 10, 21].

The nature of the deficit in avoidance responding produced by neuroleptic drugs has been the subject of considerable debate for a number of years. Some workers have suggested that neuroleptics reduce "fear" or "anxiety" and therefore reduce avoidance responding [1,19] while others have proposed that these drugs interfere with attention or sensory-arousal mechanisms so that animals cannot learn the significance of or respond to the CS [3, 14, 15, 17]. These hypotheses are not supported by the fact that neuroleptics do not impair either the acquisition or the maintenance of a conditioned emotional response, despite having powerful effects on CAR [12,13]. Furthermore, we have observed that during the presentation of the CS both haloperidol-treated and substantia nigra lesioned animals urinate, defecate and show other signs typically associated with fear in this species, suggesting that these animals are aware of and show an emotional response to the CS [8,10]. Finally, the present results with nigral-lesioned rats as well as earlier findings with neuroleptics have indicated that while these procedures prevent the acquisition of the avoidance response, they do not produce a generalized learning deficit [10].

Posluns [20] put forward the alternate hypothesis that neuroleptics (chlorpromazine) disrupt CAR by blocking or delaying the initiation of voluntary motor responses. We propose that this deficit may also be responsible for the disruption of avoidance responding observed after bilateral substantia nigra lesions. It is noteworthy that Parkinsonian patients, in whom the nigro-neostriatal dopaminergic projection has degenerated, often describe particular difficulty with the initiation of voluntary movements [22]. Also consistent with this view is the fact that nigral-lesioned animals are hypokinetic [7].

With regard to this hypothesis, the significance of the amelioration of the CAR deficit in substantia nigra lesioned or neuroleptic-treated rats by prior overtraining requires further comment. Posluns [20] demonstrated that an avoidance response in naive animals during initial training consisted of a number of discrete component acts and hypothesized that the initiation of each of these component motor responses was under voluntary control. With additional training the initiation latencies of these component responses decreased in control animals to the point where the CAR became a smooth integrated response. If it is hypothesized that the nigral lesions specifically block the initiation of voluntary motor responses, then their failure to disrupt CAR in overtrained animals could reflect a progression of the CAR response from a series of voluntarily initiated component behaviors in naive rats to a more reflexive, automatic, synthesized type of behavior in overtrained animals.

Finally, these considerations may also provide an explanation as to why bilateral 6-OHDA lesions of the substantia nigra have a selective effect on the avoidance as opposed to the escape response. Thus, while the lesioned animals may not be able to voluntarily initiate the appropriate motor patterns in response to the CS, the onset of the foot shock may induce involuntary reflexive motor responses (e.g., startle, flinch, jump, etc.) which are sufficient to begin the motor sequences required in the CAR paradigm. Here again there exists an interesting parallelism between the effects of these lesions on CAR and the syndrome observed in Parkinson's disease insofar as the remarkable ability of these patients to temporarily overcome akinesia in response to strong environmental stimuli is well documented [13].

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REFERENCES

1. Ader, R. and D.W. Clink. Effects of chlorpromazine on the acquisition and extinction of an avoidance response in the rat. *J. Pharmac. exp. Ther.* **131**: 144–148, 1957.
2. Andén, N.-E., S.G. Butcher, H. Corrodi, K. Fuxe and U. Ungerstedt. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.* **11**: 303–314, 1970.
3. Bradley, P. B. The central action of certain drugs in relation to the reticular formation of the brain. In: *Reticular Formation of the Brain*, edited by H. H. Jasper. Boston: Little, Brown and Co., 1958, pp. 123–149.
4. Cook, L. and R. T. Kelleher. Effects of drugs on behavior. *A. Rev. Pharmac.* **3**: 205–222, 1963.
5. Davies, J. A., B. Jackson and P. H. Redfern. The effect of antiParkinsonian drugs on haloperidol-induced inhibition of the conditioned avoidance response in rats. *Neuropharmacology* **12**: 735–740, 1973.
6. Evans, W. O. A new technique for the investigation of some analgesic drugs on reflexive behaviour in the rat. *Psychopharmacologia* **2**: 318–325, 1961.
7. Fibiger, H. C., H. P. Fibiger and A. P. Zis. Attenuation of amphetamine-induced motor stimulation and stereotypy by 6-hydroxydopamine in the rat. *Br. J. Pharmac.* **47**: 683–692, 1973.
8. Fibiger, H. C., A. G. Phillips and A. P. Zis. Deficits in instrumental responding after 6-hydroxydopamine lesions of the nigro-neostriatal dopaminergic projection. *Pharmac. Biochem. Behav.* **2**: 87–96, 1974.
9. Fibiger, H. C., A. P. Zis and E. G. McGeer. Feeding and drinking deficits after 6-hydroxydopamine administration in the rat: Similarities to the lateral hypothalamic syndrome. *Brain Res.* **55**: 135–148, 1973.
10. Fibiger, H. C., A. P. Zis and A. G. Phillips. Haloperidol-induced disruption of conditioned avoidance responding: Attenuation by prior overtraining or by anticholinergic drugs. *Eur. J. Pharmac.*, in press.
11. Gibbs, J., J. A. Sechzer, G. P. Smith, R. Conners and J. M. Weiss. Behavioural responsiveness of adrenalectomized, hypophysectomized and intact rats to electric shock. *J. comp. physiol. Psychol.* **82**: 165–169, 1973.

12. Herz, A. Drugs and the conditioned avoidance response. *Int. Rev. Neurobiol.* **2:** 229–277, 1960.
13. Hunt, H. F. Some effects of drugs on classical (Type S) conditioning. *Ann. N. Y. Acad. Sci.* **65:** 258–267, 1956.
14. Key, B. J. The effects of drugs on discrimination and sensory generalization of auditory stimuli in cats. *Psychopharmacologia* **2:** 352–363, 1961.
15. Killam, K. F. and E. K. Killam. Drug action on pathways involving the reticular formation. In: *Reticular Formation of the Brain*, edited by H. H. Jasper. Boston: Little, Brown and Co., 1958, pp. 111–122.
16. König, J. F. R. and R. A. Klippel. *The Rat Brain.* Baltimore: Williams and Wilkins, 1963.
17. Low, L. A., M. Eliasson and L. Kornetsky. Effects of chlorpromazine on avoidance acquisition as a function of CS–US interval length. *Psychopharmacologia* **10:** 148–154, 1966.
18. McGeer, E. G. and P. L. McGeer. Catecholamine content of spinal cord. *Can. J. Biochem. Physiol.* **40:** 1141–1151, 1962.
19. Miller, R. E., J. V. Murphy and I. A. Mirsky. The effect of chlorpromazine on fear-motivated behavior in rats. *J. Pharmac. exp. Ther.* **120:** 379–387, 1957.
20. Posluns, D. An analysis of chlorpromazine-induced suppression of the avoidance response. *Psychopharmacologia* **3:** 361–373, 1962.
21. Ray, O. S. and L. W. Bivens. Performance as a function of drug, dose and level of training. *Psychopharmacologia* **10:** 103–109, 1966.
22. Selby, G. Parkinson's disease. In: *Handbook of Clinical Neurology Vol. 6*, edited by P. J. Vinker and G. W. Bruyn. Amsterdam: North-Holland, 1968, pp. 173–211.
23. Ungerstedt, U. Brain dopamine neurons and behaviour. In: *The Neurosciences: Third Study Program*, edited by F. O. Schmitt and F. G. Worden. Cambridge: MIT Press, 1974, pp. 695–703.
24. Zis, A. P., H. C. Fibiger and A. G. Phillips. Reversal by L-DOPA of impaired learning due to destruction of the dopaminergic nigro-neostriatal projection. *Science* **185:** 960–962, 1974.