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Preoperative Operant Circling Training Facilitates Recovery Following Unilateral Substantia Nigra Lesion in Rats

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This study was undertaken to examine (1) whether pre- and/or postoperative training, using water reinforcement, to turn in circles (rotation) affects the behavioral symptoms induced by unilateral 6-hydroxydopamine (6-OHDA)-induced DA denervation of the rat substantia nigra (SN); (2) whether there was any influence of this training on the temporal pattern of recovery; and (3) whether the rotational training influences turning induced by systemic injection of dopaminergic drugs. In the first experiment, rats were trained either ipsi- or contraversive (TI or TO) to the side to be damaged 11 days before and 23 days after lesion, and tested in an open field for rotational behavior following systemic administration of apomorphine and amphetamine. In the second experiment rats were trained only before the lesion was made and tested in the open field for spontaneous circling and thigomotactic behavior. The results of the first experiment indicated maintenance of the training performance after the lesion. At the 14th day after the lesion, the ipsiversive trained group showed a higher contraversive circling frequency after apomorphine injection in relation to the contralateral trained group. In the second experiment, rats trained only before the surgery, showed asymmetrical spontaneous circling in the trained direction before and 14 days after surgery, indicating, in a drug free condition, that training direction can be restored after unilateral SN lesions, even to the contralateral body side. Moreover, thigmotactic behavior indicated a lack of habituation in an open field in unilateral lesion rats. These results indicate that (1) preoperative operant circling training can facilitate the recovery of asymmetrical motor behavior after unilateral 6-OHDA SN lesions; (2) it may interfere with DA receptor supersensitivity; and (3) habituation learning can be altered in a unilateral manner after such lesions.

INTRODUCTION

There is considerable evidence in the literature showing that pre- and postoperative experiences of an animal can reduce the behavioral effects of brain lesions (see for review Greenough, Fass, & DeVoogd, 1976; Finger & Stein, 1982). Most of the experimental studies have focused on the interaction between the level of environmental stimulation and the behavioral outcome of brain damage. In general, pre- and postoperative enrichment housing is reported to ameliorate the effects of brain lesions, although some contradictory results exist (e.g., Dalrymple-Alford, Kelche, Eclancher, & Will, 1988). Research in the field of learning and memory shows that knowledge of the environment and extended training can minimize the effects of lesions in performance of various behavioral tasks (e.g., Weese, Neimand, & Finger, 1973; Peinado-Manzano, 1987; Wilcott & Xuemei, 1990). Although motivation is one of the most important factors which determines a patient's capacity to recover after brain lesions, as indicated by Finger and Stein (1982, p. 199) "this important variable has not received adequate attention in well-controlled studies." Thus, the main purpose of this research was to study the effects of manipulations of the motivational state pre- and/or postoperatively on the behavioral reorganization after a brain lesion.

The unilateral lesion of the substantia nigra (SN) in rats is a widely used model of Parkinson's disease and has been used for studies of the mechanisms of functional recovery after neuronal injury (Pycock, 1980; Szostak, Porter, Jakubovic, Phillips, & Fibinger, 1988) as well as for the mechanisms of sensory–

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motor interactions in the basal ganglia (Steiner, Morgan, & Huston, 1985; Marshall, 1979). This lesion produces postural asymmetry and asymmetrical locomotion (e.g., Steiner, Bonatz, Huston, & Schwarting, 1988). Ipsiversive circling behavior is enhanced by systemic injection of amphetamine and contraversive after injection of DA agonists, like apomorphine. The latter effect was explained and has been used as indirect measurement of dopaminergic supersensitivity (Ungerstedt, 1971b), and can also be used to evaluate the extent of 6-OHDA lesions in the SN of rats (Neve, Kozlowski, & Marshall, 1982; Marshall & Ungerstedt, 1977; Marshall, 1979; Heikkila, Shapiro, & Duvoisin, 1981).

Circling behavior produced solely by operant training using positive reinforcement has been shown to cause DA metabolism changes, although these findings are not homogeneous (Bennett & Freed, 1986; Morgan, Yamamoto, & Freed, 1984; Yamamoto & Freed, 1982; Schwarting & Huston, 1987; Szostak, Jakubovick, Phillips, & Fibinger, 1989).

The present study was therefore designed to investigage whether the symptoms and their succedding development after unilateral SN lesions are influenced by operant conditioning of circling behavior before and immediately after surgery or only before the lesion. The advantage of this appetitively motivated paradigm is that rats can be driven to present a motor pattern similar or opposite to that induced by the lesion. Systemic administration of apomorphine and amphetamine were done in order to assess indirectly the status of the dopaminergic receptors. In addition, the second experiment evaluated functional recovery through thigmotactic behavior which has a different motor pattern than that seen in training and has also been used to evaluate asymmetry after this kind of lesion (Steiner et al., 1988).

METHODS

Animals

Sixty-seven male Wistar rats weighing 240–260 g at the time of surgery were used. They were housed individually under a 12:12 h light–dark cycle with food and water freely available. Handling was performed daily for 1 week prior to the beginning of the experiment. Water was removed from the rat's cage for 23.5 h during training and testing. The groups were designed according to the brain structure in both experiments as follows: Group TI, rats trained to turn ipsiversive to the lesion side; Group YI, rats coupled to the group TI and served as yoked controls; Group TC, rats trained to turn contraversive to the lesion side; Group YC, rats coupled to the group TC, yoked controls. Yoked controls experienced the same conditions as the trained animals, except that they did not get the reinforcement contingent to the circling behavior. Therefore, these animals received the same number of reinforcements but were not trained.

Apparatus

The training apparatus (rotometer) consisted of a 20 × 20 × 40-cm box. A water delivery magazine connected to an electromechanical control device was located on one wall. The rat was attached to a rotometer at the top of the box via a cloth jacket and a steel wire. Turns (360°) in the prescribed direction resulted in 5 s access to water. Turns in the left or right direction were automatically recorded.

Training Procedure

On the first training day, each rat was placed in the apparatus and shaped to turn in one direction by the method of reinforcing successive approximations. Thus, water was presented after 90°, 180°, 270°, and 360° turns, with a maximum of 10 reinforcers for each of these steps. The direction in which a particular rat was trained to turn was chosen randomly prior to shaping, with half the rats trained to turn left and the other half to the right side.

On subsequent days the rats were placed in the apparatus for a 20-min period during which every turn to the shaped side was rewarded. In the Experiment I, 11 training sessions before and 23 training sessions after surgery were performed. In the Experiment II, rats were trained to the preferential side after a phase of reinforcement for circling in both the left and right directions. After this phase, 11 training sessions were performed with the reinforcement being contingent only to one side (the preferred one). Training sessions were not resumed after the lesion was made.

Drugs

The 6-OHDA HCl (Sigma, USA) was dissolved in cold saline containing 0.1 mg/ml ascorbic acid to a concentration of 4 $\mu g/\mu l$. Apomorphine hydrochloride (Sandoz, Switzerland) and amphetamine sulfate (Sigma) were dissolved in sterile water. Apomorphine at a volume of 1 mg/ml and amphetamine of 2 mg/ml were injected intraperitoneally (ip), 5 min before the open field tests from the first experiment.

All drugs were prepared freshly on the day they were used.

Surgery and Histology

On the 12th day of the experiment the rats were anesthetized with sodium pentobarbital (50 mg/kg; 2 ml/kg) and their heads fixed in a stereotaxic apparatus (David-Kopf, USA). The scalp was retracted and a small hole was drilled in the skull to allow the lowering of the injection needle; the following coordinates were used: AP, 5.8; ML, 1.8; DV, 8.5 according to the atlas of Paxinos and Watson (1982). The 1.5 μl of 6-OHDA was injected at the rate of 0.5 μl/min. The injection needle was kept in place for an additional 5 min period to avoid drug reflow and then slowly was removed. After surgery, animals had free access to water and food for 24 in Experiment I and until the end of the study in Experiment II.

At the end of the experiments, the animals were anesthetized and perfused through the heart with saline followed by a 10% formalin solution. The brains were removed and kept in a 30% sucrose and 10% formalin solution until they sank (5–7 days). The brains were then frozen and cut in 50 μm coronal sections for localization of the injection site. Only rats which had the needle tip on the SN were used for data evaluation. Using this guideline, 67 of the 88 animals were ultimately included in the final statistical analysis. Additionally in the first experiment we observed that, after apomorphine injection, all included animals turned contralateral to the lesion side, on the second day after the surgery. These subjects, turned at a mean rate of 1.7 turns per minute, which has been demonstrated to be suggestive of a high degree of dopaminergic depletion (Neve et al., 1982; Marshall & Ungerstedt, 1977; Marshall, 1979; Heikkila et al., 1981).

Open Field Testing

Experiment I. On the last prelesion day and on Days 2, 6, 10, 14, 18, and 22 after the lesion, rats were injected with apomorphine 3 h after the training session in the rotometer. Five minutes after this injection they were placed into the center of the open field (circular, 60-cm diameter) and the number of full turns with a diameter smaller than 20 cm were registered by direct observation for 10 min. On the 24th day after lesion the rats were injected with amphetamine 3 h after the training session, placed in the open field, and the number of turns in both directions were registered. These tests were conducted to check the status of the dopaminergic receptors in the pre- and postlesion state.

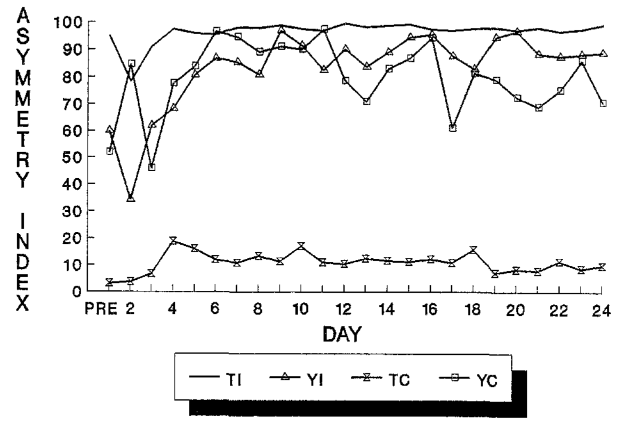

FIG. 1. Asymmetry index for all groups on the rotometer (Experiment I), operant circling behavior. Rotation is ipsilateral to the lesion side; thus, values over 50% represent ipsilateral turning and under 50% contralateral turning behavior. A 50% value means the same number of turns for both sides.

Experiment II. On the last training day, which was the prelesion day, and on the 14th day after surgery the rats were placed in a open field and recorded on videotape for 5 min between 7 and 10 PM under dim red light. The time spent on thigmotactic behavior with each side of the face and the number of spontaneous half-turns were registered from the video recordings by a person not aware of the rat's experimental group. Thigmotactic behavior or scanning was defined as locomotion along the wall with the snout less than 5 cm from the wall.

Statistics

For all comparisons, nonparametric statistical tests were used. Dependent samples were analyzed with the modified Wilcoxon rank sum test for dependent samples (Lam & Longnecker, 1983), and independent samples (trained × yoked controls) with the Mann–Whitney U test (cf. Krauth, 1983). Probabilities of $p < .05$ were considered significant.

RESULTS

Experiment I

Figure 1 shows the asymmetry index for all groups during the training sessions on the rotometer. This index (I) represents the ipsiversive turns to lesion (TI) divided by the total number of turns, ipsi- plus contraversive to the lesion side (TI + TC).

TABLE 1
Mean Number of Turns (±SEM) from Groups TI and TC in the Rotometer Session

	Group TI		Group TC	
Days	Ipsi	Contra	Ipsi	Contra
Prelesion	103.51	5.33	123.00	4.00
	±10.80	±1.20	±8.11	±1.71
Postlesion				
2	70.50	19.50[a]	90.67[a]	3.50[b]
	±13.50	±7.86	±9.46	±0.99
3	73.50[a]	7.17	87.50[a]	6.17
	±8.38	±4.88	±9.55	±2.94
4	80.50	2.16[a]	77.00	17.66[b]
	±14.93	±1.33	±14.96	±8.40
8	117.83	3.17	85.50	15.83[b]
	±8.31	±1.92	±18.10	±5.68
19	105.33	2.33[a]	85.67	6.50[a]
	±9.28	±0.76	±19.37	±2.39
24	98.17	1.17[a]	80.50	8.67
	±8.16	±0.40	±17.19	±3.76

[a] Statistically different from prelesion value.
[b] Statistically different from group TI, $p < .05$.

$$I = (TI/TI + TC) \times 100.$$

The values greater than 50% represent an ipsiversive asymmetry to the lesion side while the smaller values represent the opposite. Note that before surgery the trained groups were asymmetric while the yoked controls were not, with an index close to 50%. On the 4th day after lesion, we observed (1) ipsiversive asymmetry for yoked groups, (2) asymmetry to lesioned side and reinforced side close to 100% for group TI, and (3) asymmetry to nonlesioned but reinforced side of about 15% for group TC.

Table 1 shows the numerical data with statistical comparison for the trained groups of the same data presented in Fig. 1. Only days with significant differences are shown. It can be observed that the total number of turns are similar for both groups on the pre- and postlesion days. In addition, the number of rewarded turns were also not different between the two groups along training sessions. However, 2 days after the lesion there were significant increases in nonrewarded turns for group TI. A reversal of this tendency was observed after the 3rd postlesion day. On this day, rewarded and nonrewarded turns in both groups were similar, but on the 4th postlesion day significant differences appeared between groups TI and TC, with the former group showing a reduction in the number of nonrewarded turns and the latter group an increase. The reduction of nonrewarded turns exhibited by group TI remained until the end of the experiment. Otherwise, the increase of nonrewarded turns in group TC began to decrease on Postlesion Day 19 and was not different from the prelesion day at the end of the experiment (no statistical difference on Day 24 after lesion).

Open Field Test

Figure 2 shows the means of circling frequency induced by apomorphine or amphetamine. Positive values represent turns contraversive, and negative values represent turns ipsiversive to the lesioned side.

Before lesion no group was asymmetric. On the 2nd postlesion day and after apomorphine injection all animals turned contraversive to the lesion without any differences between them, indicating the effectiveness of lesions. The turning frequencies increased until the 10th postlesion day without any differences between the groups. On Days 14 and 18 after the lesions, the number of contraversive circling from group TI was significantly higher than from group TC. The means of amphetamine-induced circling on Postlesion Day 24 was not different between the four groups.

Experiment II

This experiment investigated the effects of only preoperative circling behavior conditioning on recovery after SN lesions, using rotation in open field and thigmotactic scanning tests as parameters for functional recovery. With this experiment we attempted to answer the questions left open in Experiment I, namely, whether functional recovery

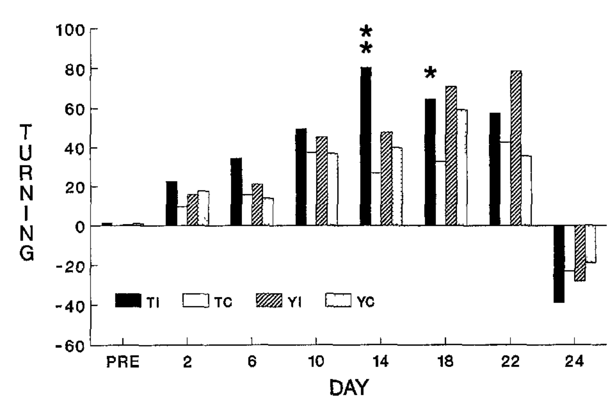

FIG. 2. Mean number of the circling behavior induced by apomorphine or amphetamine on the open field tests. Positive values represent turns contraversive to the lesion side and negative values, ipsiversive. $^{**}p < .02$; $^{*}p < .05$, between TI and TC groups.

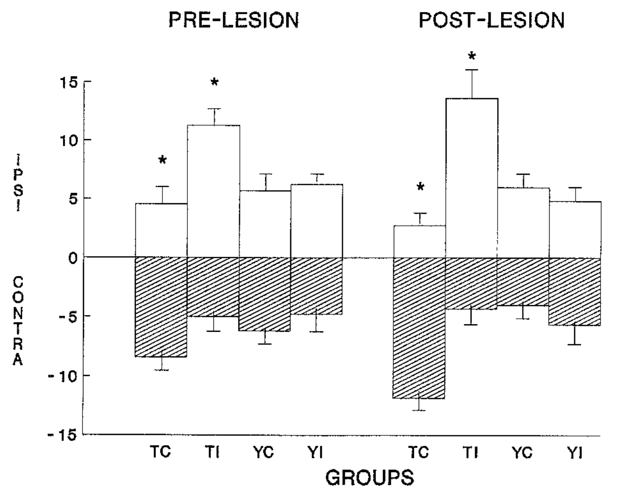

FIG. 3. Means (±SEM) of ipsiversive (positive values) and contraversive (negative values) spontaneous turning behavior on the open field tests (Experiment II). On the abscissas the groups before (left side) and after (right side) the lesion are represented. *$p < .05$, one-tailed between ipsi- versus contralateral turns.

was improved through training before or after the lesion.

Figure 3 shows the means (±SEM) of spontaneous turning behavior in the open field tests. Both trained groups presented spontaneous turning behavior to the trained side before and 14 days after the lesion was made. Yoked controls did not exhibit asymmetry in turning behavior.

Figure 4 and 5 show the mean time spent on thigomotactic behavior for circling-trained and yoked groups. The duration of locomotion along the wall with the ipsilateral and contralateral side of the lesion was not statistically different for all groups on either pre- nor on postlesion tests. It is noteworthy, however, that a significant difference was observed between pre- versus postlesion ipsilateral thigmotaxis in the first minute of testing, and that no such difference could be observed on the contralateral thigmotaxis time.

DISCUSSION

The present study investigated a possible influence of operant conditioned circling on the symptoms and their recovery after unilateral 6-OHDA substantia nigra lesion.

In the first experiment, trained rats which turned contralateral after surgery and after apomorphine injection maintained a preferential turning rate to the reinforced side even when the lesion was contralateral. In contrast, yoked controls turned ipsilateral to the lesion side as expected from the lesion effects only (Ungerstedt, 1971a). These results are different from those reported by Dunnett and Bjorklund (1983) and Szostak et al. (1988) who described a decrease of turns when the rewards were contralateral to the lesioned hemisphere. However, in these studies the rate of recovery was not investigated. Considering that the main processes of neural plasticity in this model occur in the first 2 weeks after lesion (Morgan, Huston & Pritzel, 1983; Ungerstedt, 1971a,b), it is reasonable to think that in our study operant training has been effective over neural reorganization after the lesion, even when the training was given before the lesion. It might be possible that long-lasting neuronal changes were attained by the learning process.

On the 14th postlesion day the mean of turns contraversive to the lesioned side (induced by apomorphine and out of training context) was higher for group TI than for group TC. It is known that apomorphine is a direct DA receptor agonist (Fletcher & Starr, 1987) and that rats show asymmetrical behavior to the side of lower dopaminergic activity (Ungerstedt, 1971a,b; Pycock, 1980). In fact, contraversive circling induced by apomorphine in rats with unilateral SN lesions is used as an indirect measure of DA receptor supersensitivity (Ungerstedt, 1971b). Therefore, the results of the open field tests suggest a higher supersensitivity of group TI in comparison to the other groups. This finding could indicate a greater neural reaction to the dopaminergic depletion despite the possibility that operant training leads to an imbalance (Bennett & Freed, 1986; Morgan et al., 1984; Yamamoto & Freed, 1982) or bilateral augmentation (Schwarting & Huston, 1987; Szostak et al., 1989) of DA metabolism. A summation of training and the supersensitivity process seems more conceivable considering that no difference was observed after amphetamine injection. This suggests that similar presynaptic degeneration and compensatory metabolic changes occurred. However, only a biochemical assay could clarify this issue.

Nevertheless, the findings of our Experiment I, indicate that pre- and postoperative circling training for a water reward promotes recovery of spontaneous rotation induced by the nigral lesion. These results are in good agreement with the evidence presented by others showing that pre- and postoperative experience may ameliorate or exacerbate the behavioral outcome of brain lesions (Weese et al., 1973; Greenough et al., 1976; Will, Rosenzweig, Bennett, Hebert, & Morimoto, 1977; Finger & Stein, 1982) and may extend these findings to an experimental model of Parkinson's disease.

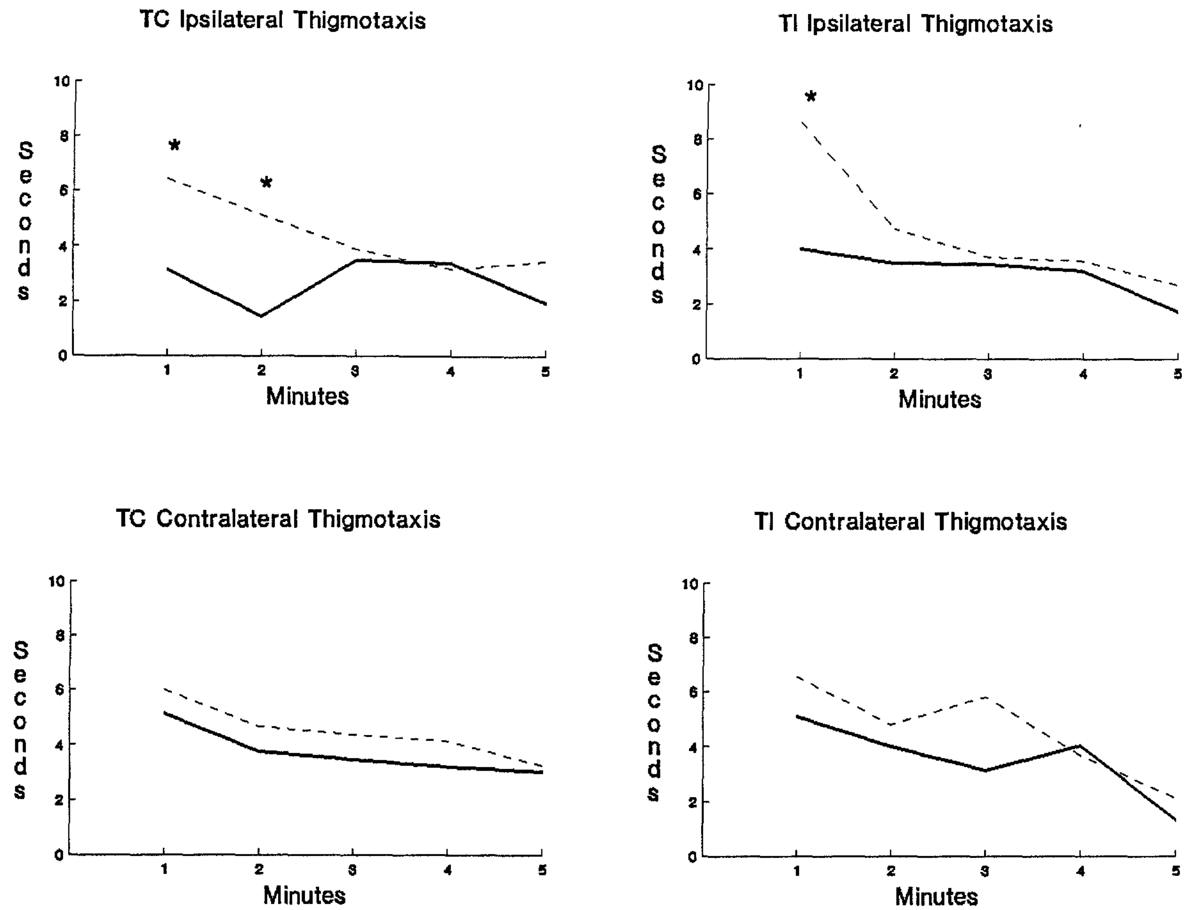

FIG. 4. Mean duration in seconds of locomotion along the wall with the ipsilateral (upper part) and contralateral side (lower part) for TC and TI groups. The total distribution throughout of the 5 min of testing, minute by minute, is shown in the abscissas, whereas the time (s) spent on thigmotactic behavior is shown in the ordinates. Lines represent thigmotactic scanning time before (dotted) and after (full) the lesion.*p < .05 (two-tailed) before versus after the lesion.

On Experiment II, the postlesion asymmetry, in the same direction of the training-induced prelesion asymmetry (contralateral for group TC) indicate a maintainence of the behavioral effects achieved only with the training procedure. Thus, we conclude that the preoperative circling training is sufficient to overcome lesion-induced turning (ipsilateral) because if recovery had occurred without training influence, the TC group would show no asymmetry as the yoked control groups. Otherwise, if the animals had not recovered they would rotate ipsilateral to lesion. This result supports the general claim that preoperative experiences can affect recovery from brain damage (see e.g., Greenough et al., 1976).

The analysis of the thigmotactic behavior, which has been used to evaluate asymmetry after this kind of lesion (Steiner et al., 1988), did not reveal an asymmetry pattern indicating a full recovery of this behavior. Interestingly, however, it was observed that all groups showed reduced ipsilateral scanning after the surgery, independent of training. This reduction was not observed for the contralateral scanning time.

The shapes of the curves for thigmotactic scanning obtained in the openfield test made before the surgery confirms the habituation tendency reported elsewhere (Huston & Bures, 1983). After surgery, in the second test session with the same environment, ipsilateral scanning seems to have habituated, since the time spent on thigmotactic scanning with this side of the face was significantly lower than in the first test for all groups. This was not observed for contralateral scanning time, suggesting a lack of habituation for this side. Considering the crossed cortical representation of sensory inputs, it is interesting to note that the lack of habituation occurred contralateral to lesion and not ipsilateral to it.

In conclusion, the present results indicate that after SN lesions (1) training just before the lesion

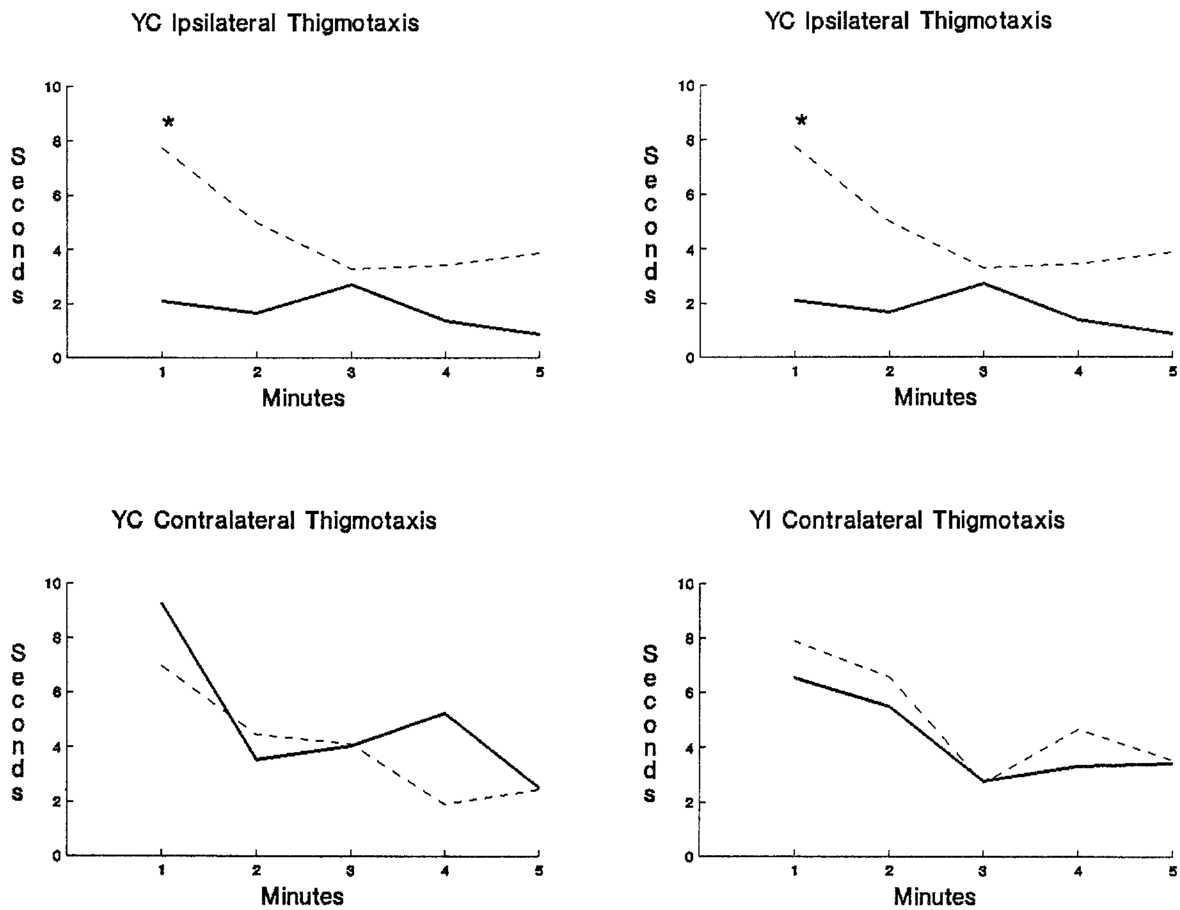

FIG. 5. Mean duration in seconds of locomotion along the wall with the ipsilateral (upper part) and contralateral side (lower part) for YC and YI groups. The total distribution throughout of the 5 min of testing, minute by minute, is shown in the abscissas, whereas the time (s) spent on thigmotactic behavior is shown in the ordinates. Lines represent thigmotactic scanning time before (dotted) and after (full) the lesion.*$p < .05$ (two-tailed) before versus after the lesion.

leads to a full recovery of spontaneous circling and thigmotactic scanning asymmetry and (2) training may influence the nigrostriatal dopaminergic system by enhancing DA supersensitivity. Furthermore, they suggest the existence of a lateralized habituation deficit as indicated by thigmotatic scanning test after the lesion.

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