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BEHAVIOURAL RECOVERY FOLLOWING TRANSPLANTATION OF SUBSTANTIA NIGRA IN RATS SUBJECTED TO 6-OHDA LESIONS OF THE NIGROSTRIATAL PATHWAY. II. BILATERAL LESIONS

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SUMMARY

Rats with a unilateral transplant of embryonic substantia nigra, placed in a cortical cavity overlying the caudate-putamen, were compared with control animals on a range of behavioral tests following bilateral 6-OHDA lesions of the ascending dopaminergic nigrostriatal pathway. Tests designed to reveal behavioural asymmetry — such as spontaneous, tail-pinch and amphetamine-induced rotation, sensorimotor orientation, and side preference in a T-maze — revealed that the rats with bilateral 6-OHDA lesions and a unilateral transplant were similar to unilaterally lesioned animals with one intact nigrostriatal pathway. Both transplanted and bilaterally lesioned control rats became spontaneously akinetic after the second 6-OHDA lesion. This akinesia could be reversed by a low dose of amphetamine (0.5 mg/kg) in the transplanted but not in the non-transplanted control rats. The attenuated effects of apomorphine and L-DOPA on activity and rotation suggest that the nigral transplant produced a partial reversal of receptor supersensitivity following the 6-OHDA lesion on the same side as the transplant. However, other effects of the bilateral 6-OHDA lesion, including the development of aphagia, adipsia and akinesia, were not reversed by the presence of the transplant. The transplants were shown by fluorescence histochemistry to have densely reinnervated the dorsal parts of the denervated caudate-putamen on the side ipsilateral to the transplant. The results show that intracortical nigral grafts reinnervating parts of the dorsal caudate-putamen can reverse some, but not all, functional impairments associated with bilateral destruction of the nigrostriatal pathway.

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INTRODUCTION

Bilateral destruction of the dopaminergic nigrostriatal pathway produces a well characterized syndrome, similar to that induced by lateral hypothalamic lesions, involving, aphagia, adipsia, akinesia and bilateral sensory neglect[1,3,10,13,14,17–20,22].

The transplantation of embryonic substantia nigra to a site overlying the caudate-putamen has previously been shown to provide a dopaminergic reinnervation of the 6-OHDA-denervated caudate-putamen, which is capable of reversing many features of the unilateral 6-OHDA syndrome[2,3,7,16]. The first study of the ability of such nigral transplants to reverse the effects of *bilateral* lesions was disappointing: the transplant animals died even more rapidly than the control group, and their performance in a sensorimotor test battery yielded greater impairments than the controls[3]. However, the interpretation of these findings was ambiguous since subsequent biochemistry revealed suboptimal lesions in several animals of the small control group.

The present experiments provide a more extensive analysis of the functional consequences of a unilateral nigral transplant on the behavioural impairments following bilateral 6-OHDA lesions. Furthermore, since the bilaterally lesioned animal is spontaneously akinetic, the effects of both non-pharmacological (tail-pinch) and pharmacological (amphetamine, apomorphine, L-DOPA) activation on various behaviours were investigated. As was found following unilateral lesions[7], the transplant can fully replace the destroyed ipsilateral pathway in bilaterally lesioned rats in certain tests (e.g. rotation, sensorimotor performance and spontaneous choice behaviour in a T-maze), resulting in an animal indistinguishable from one with a unilateral lesion, whereas on other tests (e.g. aphagia, adipsia and akinesia) no transplant-induced reversal of the impairment was found. Parts of the present data have previously been reported in preliminary form[4].

MATERIALS AND METHODS

Subjects

Forty-six adult female Sprague–Dawley rats (Anticimex AB, Stockholm, Sweden) were employed in the present experiments. All rats had previously been employed in a study of the transplant-induced reversal of the behavioural deficits following unilateral 6-OHDA lesions[7].

Design

All animals received unilateral 6-OHDA lesions of the right nigrostriatal pathway and cortical cavities, and 28 animals additionally received transplants of the embryonic substantia nigra, as reported in detail in the accompanying paper[7]. In the present experiments, the animals were tested in two batches. In the first batch, 14 transplant animals and 10 controls received a second 6-OHDA lesion, identical to the first[7], in the intact (left) nigrostriatal pathway, 4 months after the initial lesion (3 months post-transplantation). Behavioural testing was conducted over a 10-day period immediately following the bilateral lesion. In the second batch, 14 transplant animals

and 8 controls received a second 6-OHDA lesion to the contralateral nigrostriatal pathway 7 months after the initial lesion (6 months after transplantation). Most animals in this batch were successfully kept alive by intragastric tube-feeding for a period of 8 weeks, and behavioural testing was conducted throughout this period.

Post-operative care and monitoring

Following contralateral lesion, rats were housed individually. Body weight and the weight of the water bottles were recorded daily. In the first batch of animals, intragastric intubations of wet-mash and subcutaneous injections of isotonic saline were given from the fifth post-operative day to animals remaining totally aphagic and adipsic, via a slightly curved stainless steel tube with rounded ball tip. In the second batch, all animals were tube fed a high-energy liquid diet preparation (Vivonex, Vitrum, Sweden), commencing on the second post-operative day. The diet was administered intragastrically 3–4 times daily via a thin flexible polyethylene tube. In addition to dry pellets, all animals were given wet wheatmeal bread freely available in the home cage, and the daily amount eaten was recorded.

Activity

Activity testing was conducted in an Animex activity meter, and total counts over a 10-min period were recorded. The first batch of animals was tested for spontaneous activity prior to, and 1, 3 and 5 days following the bilateral lesion. Rats were tested under tail-pinch activation on the 6th post-operative day by attaching a paper clip to the tail 2–3 cm from the tip. On day 7, rats were tested under 0.5 mg/kg metamphetamine, approximately 20 min after the injection. The second batch of animals was tested on days 5, 11 and 19 post-lesion for spontaneous, tail-pinch, and amphetamine-induced activity, each test separated by at least 2 h. They were additionally tested under 0.05 mg/kg apomorphine on day 40, and under 5 mg/kg L-DOPA on day 42.

Rotation

Rotation testing was conducted in the rats of the second batch in hemispheric perspex bowls supported on metal rings, as described previously[2,3,7,23]. Spontaneous and tail-pinch-induced rotation were recorded for continuous 3-min periods, during which the total number of quarter turns were recorded separately for either direction. The two tests were separated by approximately 10–15 min, and conducted on days 5, 11, 19 and 26 post-operatively. Rotation to 5.0 mg/kg metamphetamine was tested on days 10 and 54, by sampling 1-min intervals every 10th min over 1 h, and recording full turns in either direction. Rotation to 0.05 mg/kg apomorphine was tested on days 13, 32 and 55 by sampling 2-min intervals every 10th min over 30 min, recording quarter turns in either direction. Rotation to 40 mg/kg L-DOPA was tested on day 33, by sampling 2-min intervals every 15 min over 90 min and recording quarter turns in either direction.

Sensorimotor test battery

The sensorimotor test battery was modified from that developed by Marshall[12,14], and has previously been described in detail[3,7]. Briefly, the battery involved 'orientation' and 'limb use' components, rating the accuracy of orientation to various lateralized stimuli, and the coordinated use of the individual limbs in a variety of grasping, placing and withdrawal reflexes, respectively. The first batch of animals was tested under spontaneous levels of activation on days 1, 3 and 7 following lesion, and under tail-pinch on day 5. The second batch of animals was tested under spontaneous, tail-pinch and 0.5 mg/kg amphetamine during the 8th week of survival, each test being conducted on a separate day.

T-maze

The second batch of animals was tested for arm preference in an unbaited T-maze of conventional design, under both tail-pinch and amphetamine activation. Each animal received 3 tests under 0.5 mg/kg amphetamine (days 6, 8 and 12), and 3 under tail-pinch (days 25, 27 and 31). Each test comprised 2 trials separated by approximately 10 min. On each trial the rat was allowed 2 min to run the maze, followed by a gentle push for those animals that had not left the start arm. If the rat failed to move through the maze after a further minute it was removed. When an animal chose between the two side arms, the side of choice was recorded.

Fluorescence histochemistry

Approximately half the animals of the first batch, and the majority in the second batch survived to the end of behavioural testing and were sacrificed for fluorescence histochemistry, using the ALFA method (procedure I)[11].

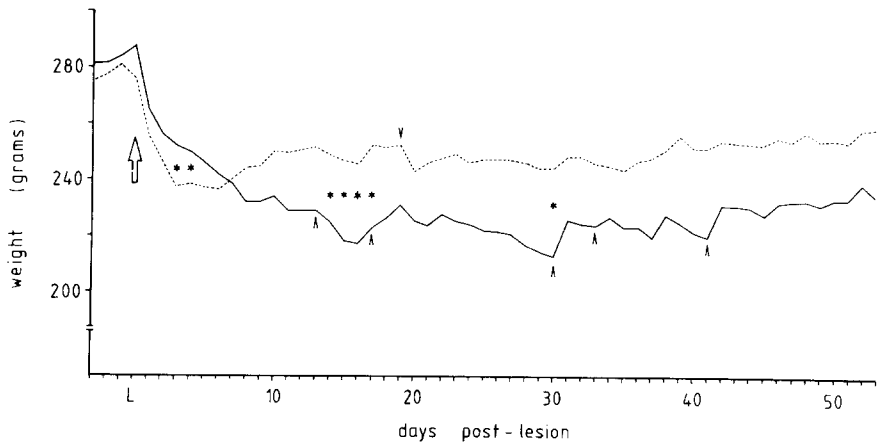

Fig. 1. Mean body weights of the transplanted (solid line) and control (dashed line) rats over the 3 days preceding and 53 days following the second 6-OHDA lesion (L, open arrow). Days on which an animal of either group died are indicated by an arrow head. Days on which the mean body weights of the two groups differed ($P < 0.05$) is indicated by a *. Although water, laboratory chow and wet bread were freely available, all animals, apart from one of the transplanted group, additionally required intragastric tube feeding throughout the test period (see text).

RESULTS

Survival: aphagia and adipsia

In the first batch, 3 animals in the transplant group commenced drinking 2, 4 and 5 days after the bilateral lesion, and these animals started eating dry pellets spontaneously at the same time. No other animal in either group recovered from severe aphagia and adipsia over the course of the experiment. Six transplanted and 5 control rats had died by day 11, when surviving animals were sacrificed for fluorescence histochemistry.

In the second batch, force-feeding was more successful: 9 (of 14) transplant and 7 (of 8) control animals survived the full 8 weeks of testing. The mean weights of each group are shown in Fig. 1. The control group initially lost weight faster than the transplant rats, but after 7 days they showed an upturn and stabilized at a higher body weight than the transplant rats. All surviving rats were aphagic and adipsic throughout the test period, and were dependent upon tube-feeding for survival, although the controls in general appeared healthier than the transplant rats and were given a lower mean daily volume of liquid diet. Nevertheless, most rats drank and ate a little. Bread and water consumption of surviving animals was significantly greater in the control group (Mann-Witney, U = 8 and 6, respectively; $P < 0.01$ in each case).

Akinesia

The activity scores of the first and second batches of animals under each test condition are shown in Table I. Where repeated identical tests do not differ, each rat's counts have been combined to give a mean score. In neither batch did the transplant animals differ from controls in spontaneous akinesia. Tail-pinch had a marked activational effect on all rats, but only in the first batch, tested 6 days after lesion, did tail-pinch have a greater effect on the transplant animals than the controls ($t = 2.34$ with 22 df, $P < 0.05$). The activity levels reinstated by tailpinch in the transplanted rats in batch one, and in both transplanted and control rats in batch two, was similar to the spontaneous activity recorded prior to the second lesion (cf. Table I).

TABLE I

Spontaneous, tail-pinch and drug-induced activity counts of bilaterally lesioned transplanted and control rats

The first batch was tested during the first week following the second 6-OHDA lesion, whereas the second batch was tested 2–8 weeks post-operatively. —, not tested, * $P < 0.05$.

	First batch		*Second batch*	
	Control	*Transplant*	*Control*	*Transplant*
Before 2nd lesion	232.3 ± 20.4	269.4 ± 28.7	—	—
Spontaneous	25.5 ± 4.0	44.0 ± 9.3	79.5 ± 23.6	62.6 ± 6.4
Tail-pinch	103.2 ± 25.1	193.1 ± 27.1*	274.5 ± 31.6	251.7 ± 15.6
Amphetamine 0.5 mg/kg	209.0 ± 25.1	425.3 ± 30.9*	65.5 ± 29.2	210.8 ± 43.6*
Apomorphine 0.05 mg/kg	—	—	440.7 ± 24.7	294.2 ± 48.2*
L-DOPA 40 mg/kg	—	—	437.0 ± 40.6	298.7 ± 68.3

In both batches, amphetamine had a greater activational efect on transplant rats than on controls ($t = 3.95$ with 22 df, $P < 0.001$, and $t = 2.35$ with 17 df, $P < 0.025$, respectively). At 7 days (in batch one) and 5 days (in batch two) after the second lesion, amphetamine activated both the transplanted and the non-transplanted control rats. However, when tested at 11 and 19 days post-lesion, 0.5 mg/kg amphetamine no longer had any effect on the non-transplanted controls. By contrast, the activational effect of amphetamine remained in the transplanted rats ($t = 2.32$ with 17 df, $P < 0.025$, when compared with controls). In the second batch, apomorphine and L-DOPA both produced a greater activation in the control rats, although this was only significant under apomorphine ($t = 2.29$ with 16 df, $P < 0.025$).

Rotation

Spontaneous turning. Both the transplanted and control rats showed spontaneous turning away from the intact side (towards the right) prior to the second lesion. As described in the previous report[7], tail-pinch activation eliminated this asymmetry in the transplanted but not in the control rats (left columns in Fig. 2). When the rats were tested 1–3 weeks following the second lesion the non-transplanted control animals showed no asymmetry, whereas the transplanted rats now expressed a high degree of rotation away from the side of the transplant (i.e. towards the left). Since turning rates did not differ over the 4 test sessions the scores were combined over the 4 days. In Fig. 2, the rate of turning away from the first-operated side (towards the left), as a proportion of total turns, is given before and after the second lesion in the non-transplanted controls (open columns) and in the transplanted rats (hatched columns). After the second lesion, tail-pinch increased the total turning rate (both left and right) in both groups, but had no effect on the symmetry of the bilaterally lesioned controls nor on the degree of bias of the bilaterally-lesioned transplanted animals (right columns in fig. 2). The difference between transplanted and control animals was significant, both with and without tailpinch activation (spontaneous: $t = 3.22$; tailpinch: $t = 2{,}72$; with 19 df, $P < 0.01$ in each case).

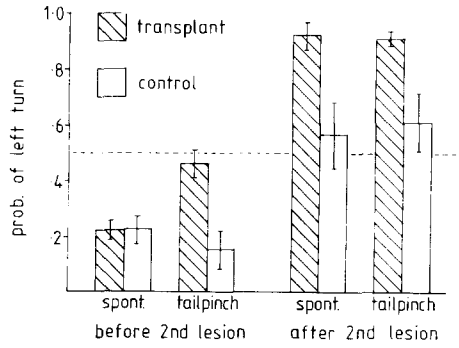

Fig. 2. Spontaneous and tail-pinch-induced rotation in transplanted and control rats before and after the second, left 6-OHDA lesion. Values are the mean probability of a left turn (towards the second lesion, away from the transplant) ± S.E.M.

Amphetamine-induced turning. The transplanted rats included in the present experiments all showed compensation of the inital amphetamine-induced turning response. As shown in Fig. 3A (filled circles) the turning response had been reduced from a mean of 15.3 right turns/min prior to transplantation to a mean of 0.5 left turns/min 1–2 weeks before the second lesion (i.e. at 6 months after transplantation). By contrast, the turning rate remained high in the non-transplanted, lesioned control rats (open circles in Fig. 3A). Following the second 6-OHDA lesion, the transplanted rats exhibited strong turning towards the left (i.e. in the direction away from the side of the transplant) whereas the strong turning response in the control rats was totally abolished (Fig. 3A). Thus, 10 days after the second lesion, the contralateral turning rate was increased from 0.5 to 11.4 turns/min in the transplanted animals and the ipsilateral turning of the controls was reduced from 15.2 to 1.0 turns/min ($t = 8.39$ with 13 df, and $t = 7.17$ with 7 df, respectively, $P < 0.001$ in each case).

Apomorphine and L-*DOPA induced turning.* Prior to the second lesion, the non-transplanted unilaterally-lesioned controls turned contralaterally in response to 0.05 mg/kg apomorphine with a mean rate of 3.9 turns/min, whereas the transplanted rats exhibited no, or only very weak, asymmetry (Fig. 3B; cf. ref. 7). Following the second 6-OHDA lesion, the transplanted rats gradually developed a strong turning response towards the transplant side, and the control rats manifested an augmented response in the opposite direction (Fig. 3B). On all 3 apomorphine tests, all controls maintained strong rotation towards the second lesion, whereas transplanted animals showed strong rotation in the opposite direction ($t = 5.81$ with 19 df, $t = 5.44$ with 16 df, and $t = 8.43$ with 13 df, respectively, $P < 0.001$ in each case). 40 mg/kg L-DOPA induced a pattern of rotation similar to apomorphine: all controls turned strongly towards the side of the second lesion, whereas all but one transplant rat showed strong turning away from the lesion and towards the side of the transplant ($t = 4.96$ with 10 df, $P < 0.001$).

Sensorimotor tests

The mean scores on the sensorimotor test battery for transplanted and control rats of the first batch on each day of testing are shown in Fig. 4A. As reported in the preceding paper[7], both groups showed asymmetry in orientation scores prior to the second lesion, failing to attend to stimuli contralateral to the unilateral lesion, whereas only a slight asymmetry was apparent in the limb use scores. Following the bilateral lesion, limb use scores were slightly higher on the side ipsilateral to the second lesion, but no differences were found due to tail-pinch activation or between the groups. On the orientation component, by contrast, not only were scores higher in the transplanted rats on the left side (ipsilateral to the second lesion, contralateral to the transplant, main side effect, $F = 48.00$ with 1,22 df, $P < 0.001$), but tail-pinch enhanced responding in the transplant group alone (main day effect, $F = 5.78$ with 3,66 df, $P < 0.002$; group $\times$ day interaction, $F = 3.37$ with 3,66 df, $P < 0.025$).

The second batch of rats was tested 8 weeks following bilateral lesion (Fig. 4B). The limb use component again failed to differentiate between the groups. On the orientation component, the controls had equivalent scores for the two sides of the

body, whereas transplant rats had markedly enhanced scores on the left contralateral to the transplant, and correspondingly reduced scores on the right (main side-effect, $F = 35.78$ with 1,14 df, $P < 0.001$; group $\times$ side interaction, $F = 61.83$ with 1,14 df, $P < 0.001$). No significant differences were found between the spontaneous, tail-pinch and amphetamine-induced activation conditions. The performance of the transplanted rats with bilateral 6-OHDA lesions on the orientation component is remarkably similar to that of unilateral lesioned controls, either of the first batch prior to second lesion (Fig. 4A, condition 'U'), or of the larger groups analyzed in the previous report[7].

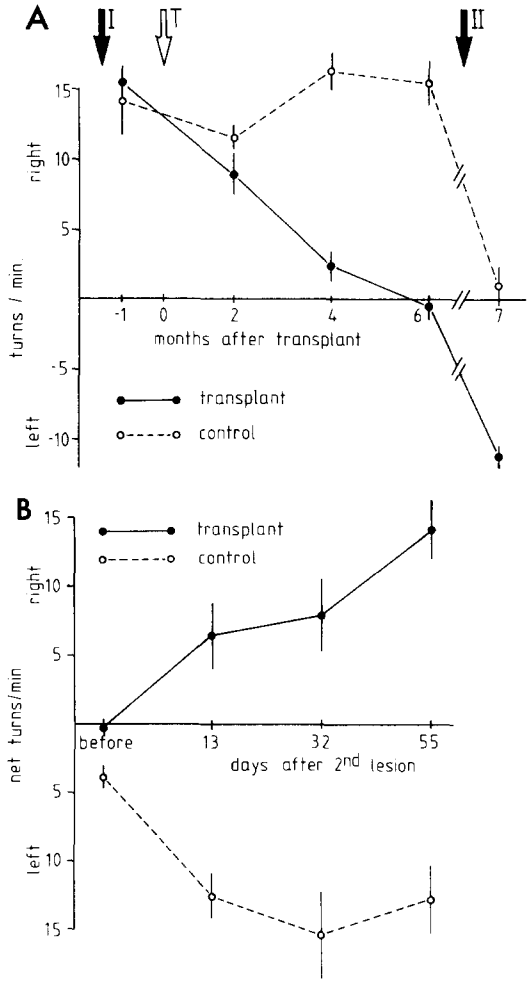

Fig. 3. A: amphetamine-induced rotation in transplanted and control rats. All animals received the first, right 6-OHDA lesion (solid arrow I) one month prior to transplantation surgery in the experimental group (open arrow). Further amphetamine tests were conducted 2, 4 and 6 months following transplantation, followed by the second, left 6-OHDA lesion (solid arrow II), and the final test administered 10 days later. B: apomorphine-induced rotation in transplanted and control rats prior to and 13, 32 and 55 days following the second, left 6-OHDA lesion. Values in each case are mean net turns/min $\pm$ S.E.M.

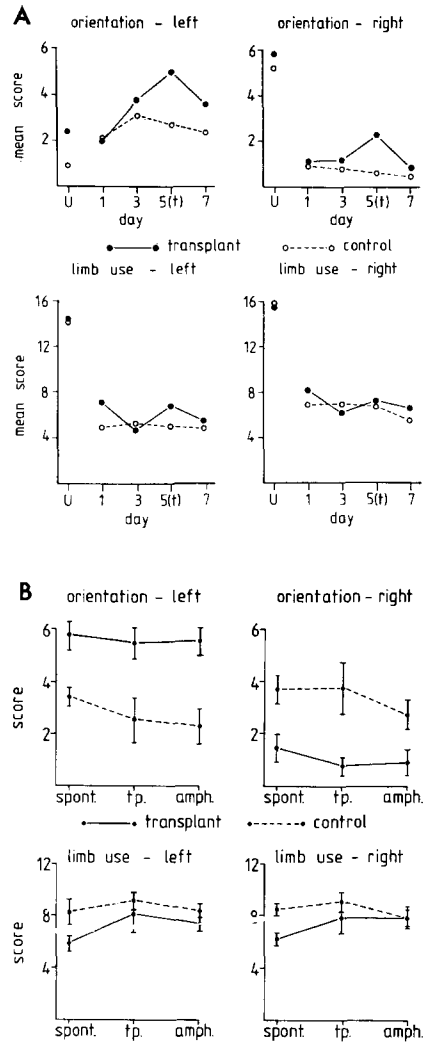

Fig. 4. Sensorimotor test scores of the transplanted and control animals in the two batches. A: the first batch prior to (U), and 1, 3, 5 and 7 days following the second, left 6-OHDA lesion. On day 5, all animals were tested with tail-pinch (t); all other tests were conducted under a spontaneous level of activation. B: animals of the second batch, tested 7 weeks following the second, left 6-OHDA lesion. Animals were tested under spontaneous, tail-pinch and 0.5 mg/kg amphetamine-induced activation. In each case, mean scores ± S.E.M. are given separately for the left and right sides on the orientation and limb use components of the battery.

T-maze

All animals ran the maze on all trials under tail-pinch activation. By contrast amphetamine failed to activate the animals sufficiently to run the full length of the maze on a total of 8 trials for each group. Prior to the second lesion the controls had turned left, contralateral to the unilateral lesion on only 3% of of the trials, whereas the transplanted animals had turned left on 32% of occasions (left columns in Fig. 5).

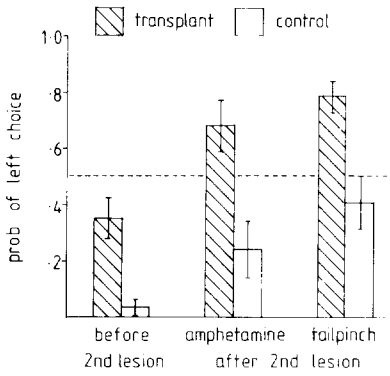

Fig. 5. Spontaneous side choice in an unbaited T-maze, before the second, left 6-OHDA lesion, and under tail-pinch and 0.5 mg/kg amphetamine-induced activation following the second lesion. Values are the mean probability of a left choice (towards the second lesion, away from the transplant) ± S.E.M.

Following the bilateral lesion (right columns in Fig. 5), the controls turned left with a probability of 24% under amphetamine and 41% under tailpinch activation, which in the latter case did not differ significantly from a symmetrical 50% score ($t = -2.53$ with 7 df, $P < 0.02$, and $t = -0.97$, NS, respectively). By contrast the transplant groups showed a significant bias to choose the left arm, contralateral to the transplant under both conditions (tail-pinch: 79% left choices, $t = 5.25$, with 10 df, $P < 0.001$; amphetamine: 68% left choices, $t = 2.01$ with 10 df, $P < 0.05$).

Fluorescence histochemistry

Histofluorescence analysis was obtained from 3 of the controls and 8 of the transplanted rats in the first batch, and from all 8 controls and from 13 of the transplanted rats in the second batch. The remaining animals died during the course of the experiments, and their brains were not retrieved sufficiently rapidly.

In the *bilaterally lesioned controls*, 5 of the 11 rats had complete, bilateral denervation of all forebrain areas analyzed. In 3 further rats the entire head of the caudate-putamen was devoid of dopamine fibres on both sides, whereas a sparse to moderately dense terminal plexus remained in parts of the olfactory tubercle, nucleus accumbens and the septum, on one side. These rats were all severely aphagic and adipsic, and consumed less than 2 ml of water per day. The remaining 3 rats had parts of the dopaminergic innervation left in the caudate-putamen on the second lesioned side. Two of these rats consumed significant amounts of water (up to 9–10 ml per day). They did, however, require tube-feeding throughout the 55 day experimental period.

In the *transplanted rats*, the denervation was complete on both sides in 16 of the 21 specimens analyzed. In 4 of the remaining specimens, part of the dopamine innervation was spared in the medial parts of the olfactory tubercle, nucleus accumbens and bed nucleus of the stria terminalis and septum on one side. In the fifth remaining specimen, a substantial terminal plexus remained in the lateral and ventral parts of the head

of the caudate-putamen on the second lesioned side. In contrast to the others, which all developed severe aphagia and adipsia, this rat showed only a transient impairment: after one week it drank about 20 ml water per day, and thereafter maintained body weight without tube feeding.

All transplanted rats analyzed possessed surviving dopamine-rich transplants, and in all cases the transplants were found to have reinnervated part of the underlying caudate-putamen. The dopamine ingrowth was confined to the dorsal part of the neostriatum, and the area covered by the newly-formed fibres varied from about 1/10 to 1/3 of the head of the caudate-putamen. The extent of ingrowth into the caudate-putamen in each transplant rat was rated blind, in an identical manner to that adopted in a previous study[3], and the ingrowth was compared with the behavioural performance of the transplant animals. In only one of the present tests — amphetamine-induced locomotor activity — was a significant correlation found between the degree of ingrowth and performance (Spearman's rho $= +0.63$, $P < 0.05$).

DISCUSSION

In previous studies, it has been shown that dopamine-rich nigral transplants can reinnervate the denervated neostriatum, and that such transplants can reverse many of the functional impairments associated with unilateral 6-OHDA-induced destruction of the nigrostriatal pathway[2,3,7,16]. The present study has investigated in more detail the effects of nigral transplants in animals with bilateral 6-OHDA lesions of the nigrostriatal pathway, and has found that such transplants can indeed have substantial ameliorative properties in a range of behavioural tests.

All tests of asymmetry between the two sides of the animal revealed differences between transplanted and control rats with bilateral 6-OHDA lesions. Following the second lesion, the non-transplanted control animals showed equal levels of responding to the two sides on spontaneous, tail-pinch and amphetamine-induced rotation, and in the T-maze they manifested equal side preference when tested under tail-pinch activation. On all these tests, the transplanted animals showed a strong left bias, contralateral to the side of the transplant. A similar pattern of results is seen in sensorimotor orientation in the long-term experiments (i.e. the second batch of animals). Whereas the controls were equally inattentive to the two sides of the body, the transplanted rats showed increased orientation to the left side, contralateral to the transplant. Interestingly, the increased attention to the left was matched by a decrease in orientation to the right side, and results in scores remarkably similar to the asymmetry manifested by unilaterally-lesioned rats (cf. Fig. 4A and ref. 7). These results suggest that the sensorimotor test battery does not provide scores for the two sides of the body independently, but that a competitive interaction takes place, such that when an animal has an orientational bias to one side, attention to stimuli on the contralateral side are ignored to a greater extent than if no such bias exists.

In the apomorphine-induced rotation tests, prior to the second lesion, the control animals turned to the left (i.e. away from the denervated side), whereas the transplanted rats showed no rotational asymmetry. This is compatible with the interpretation that a dopaminergic reinnervation of the caudate-putamen from the trans-

plant can block the development of receptor supersensitivity manifested by turning in the control rats following unilateral 6-OHDA lesions[7,15,21]. Following the second lesion, the strong turning to the right by the transplanted animals under apomorphine is compatible with the development of supersensitivity in the left caudate-putamen (i.e. on the non-transplanted side). However, the strong augmentation of turning to the left by the control rats following the second lesion was unexpected, although was manifested by every animal in the non-transplanted group.

In the tests of rotation, sensorimotor orientation, and side bias in the T-maze, the bilaterally lesioned rats with a unilateral transplant produced remarkably similar asymmetry scores to the control rats with unilateral lesions (compare with present data and ref. 7). Thus a dopaminergic reinnervation of the caudate-putamen from an ectopic graft, which itself presumably does not receive a normal afferent input, can nevertheless reinstate those aspects of neostriatal function implicated in the organization of responding to lateralized stimuli, suggesting that the nigrostriatal DA input mediates a 'permissive' role in the striatum, rather than one involving the relay of specific information[4,17]. Nevertheless, following the second lesion, all animals were spontaneously akinetic. In the first post-operative week, amphetamine provided a partial activation of the control animals, although this was not as great as that seen in the transplanted rats. This effect was short-lasting in the controls, and at longer times post-lesion only the transplanted group was activated by amphetamine. Conversely, apomorphine induced higher levels of locomotor activity in the control animals, again suggesting that the reinnervation from the transplant can block the development of supersensitivity in denervated dopamine terminal areas. Since the reinnervation from the transplant is restricted to the dorsal striatum, these results are difficult to reconcile with the finding that 6-OHDA-induced destruction of dopamine terminals in the nucleus accumbens rather than in the caudate-putamen have been particularly implicated in the disruption of the locomotor response to dopaminergic drugs[5,9].

Several other behavioural measures, and particularly the aphagia, adipsia and akinesia induced by the bilateral lesion, were not found to be ameliorated by the transplant. Whereas the present study employed a serial procedure for making bilateral 6-OHDA lesions in transplanted and control rats, the animals were found to be as impaired as has been reported following the more commonly adopted one-stage procedure[14,17,22]. The histofluorescence analysis of animals that had less than total bilateral dopamine depletions suggests that these results may be due to the failure of the dorsal reinnervation to reach other segments of the neostriatum critical in the mediation of eating and drinking behaviours. The two control and one transplanted rat which showed substantial eating and drinking in the post-operative period were all found to have a common residual terminal plexus spared by one of the two lesions in the ventral and lateral parts of the neostriatum. Both 6-OHDA[8] and kainic acid[6] lesions of this area have been found to result in aphagia and adipsia. If this interpretation is valid then a different transplant placement, permitting reinnervation of the ventral striatum, should be able to reverse functional impairments not influenced by the present graft placement in the dorsal parietal cortex; a study of this is currently in progress.

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