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# Behavioral Effects of Neural Transplants Into the Intact Striatum

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LU, S. Y., M. GIORDANO, A. B. NORMAN, M. T. SHIPLEY AND P. R. SANBERG. *Behavioral effects of neural transplants into the intact striatum.* PHARMACOL BIOCHEM BEHAV **37**(1) 135–148, 1990.—The behavioral effects of fetal brain tissue and adrenal medulla transplants into the intact striatum of rats were investigated. Following a bilateral injection of 1.5, 3 or 6 μl of fetal striatal tissue, a volume-related weight loss was found in all transplanted groups, including the SHAM group, during the first 7 days after the surgery. Rearing behavior was changed in a transplant volume-related manner. Histological analysis suggested that the locomotor effects of transplants into the intact striatum are related to the volume of the transplants. Following bilateral transplantation of fetal cortex (CTX), substantia nigra (SN), striatum (STR), or adrenal medulla (AM) into the striatum, the different behavioral deficits were observed among these transplant groups. The SN group showed a decrease in spontaneous locomotion, significantly increased rearing activity in response to administration of amphetamine, reduction of food intake and water intake and a reduction in body weight. The CTX and AM groups showed a marked increase in spontaneous rearing activities. Hyporesponsiveness to the administration of apomorphine (1 mg/kg) and amphetamine (1 mg/kg) was evident in the CTX, STR, AM groups and SHAM groups. In contrast, the haloperidol-induced catalepsy scores of the CTX, STR, SN and AM were significantly higher than those of a normal control group. In addition, the CTX group showed a deficit in the delayed reward alternation test. These results indicated that the behavioral deficits produced by transplants into normal striatum may be related to both mechanical destruction due to transplant expansion and specific neurochemical interactions of each tissue type between the host and the transplant. Therefore, potential negative consequences of neural transplantation therapy should be considered as well as the beneficial effects.

Neural transplants Striatum Substantia nigra Cortex Adrenal medulla Behaviors Locomotor activity Dopamine

NEURAL transplantation research has provided a potential therapy for neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and Huntington's disease (HD). During the past several years, research by various groups has shown that transplanted neural tissue into an animal model of HD survives, forms connections with the host brain (22), and ameliorates the behavioral deficits caused by a variety of CNS lesions (8, 9, 17, 21, 22, 29, 37)

Although clinical trials utilizing transplants in Parkinson's patients appear promising, animal research has also revealed the complexity of transplantation and possible adverse effects on the host (4,7). For example, Dunnett *et al.* (13) examined the effects of fetal cortical transplants on the behavioral deficits produced by aspirative prefrontal lesions. The animals which received both lesions and transplants demonstrated a greater impairment in T-maze alternation, spatial navigation and locomotor activity than those which received lesions only. In a similar study, Amemori *et al.* (1) revealed that neural transplants enhanced rather than reduced the impairment of spatial memory and olfaction in bulbectomized rats. These data indicated that the transplant had not only failed to repair the lesion-induced damage but actually exaggerated the deficits. These findings suggested that transplants can have both a positive (i.e., correcting behavioral deficits) and negative effect (i.e., exaggerating the functional deficits following damage).

Studies on the behavioral effects of neural transplantation have emphasized the recovery of lesion-induced behavioral deficits, while the perturbations induced by the transplant have been given relatively little attention. The behavioral manifestations resulting from transplantation depend on complex interactions between the transplant and the host. These include the host's capacity to accommodate to the trauma of the transplant surgery, its ability to adapt to the invasion of foreign material, and the ability of the transplant to integrate functionally with the existing host circuitry. Therefore, the study of the traumatic effect of transplants in an intact host brain has both neurobiological and clinical significance.

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Deckel *et al.* (8, 10, 11) and Hagenmeyer-Houser *et al.* (19) transplanted fetal striatal tissue into normal rat striatum and studied the locomotor effects of the transplant. They found "lesion-like" locomotor deficits which were similar to the locomotor hyperactivity induced by excitotoxin lesions of the striatum. The present study was designated to further examine the abnormal behaviors resulting from the transplantation of fetal brain tissue into normal rat striatum.

In this study, we examined the possibility that 1) the transplant-induced abnormalities were related to the volume of the transplant, and 2) transplants from various neural regions, which contain different neuronal populations and neurotransmitters, exert different behavioral effects on the host.

## EXPERIMENT 1

It has been previously found that abnormal behavior can result from the transplantation of fetal striatal brain tissue into normal rats (8–11, 19). The present experiment was designed to examine the effect of the volume of the transplanted tissue on locomotor behavior and the regulation of body weight.

### METHOD

#### *Subjects*

Adult male Sprague-Dawley (Zivic Miller) rats (n = 43) weighing 250–300 g were used in the following studies. All animals were housed individually in a room maintained on a 12-hour light-dark cycle (lights on at 06.00 hours). Food and water were available ad lib.

#### *Transplantation Surgery*

The rats were divided into five groups. The three transplant groups received bilateral transplants of embryonic striatum (gestation day 15–17) into their intact striata using three different volumes: 1.5 μl (n = 7), 3 μl (n = 9) and 6 μl (n = 9). The SHAM group (n = 9) received 6 μl of lactated Ringer's solution only. The normal control group (n = 9) consisted of unoperated rats.

The techniques for tissue preparation and transplant procedures have been described in detail (3,7). Briefly, fetal striatal tissue was obtained from commercially purchased time-pregnant female rats (Zivic Miller). Under sodium pentobarbital (40 mg/kg) anesthesia, a laparotomy was performed in order to expose the uterus, and embryos were then extracted individually. After the removal of the cranium and overlying integument, the fetal brain was removed and submerged in a dissection dish containing lactated Ringer's solution. Under a dissecting microscope, the cortex was peeled laterally and the half-moon-shaped fetal striatal tissue was removed. The dissected fetal striatum was then aspirated into a capillary glass needle (25⅝ ga) connected to a Hamilton syringe (50 μl) and then stereotaxically delivered into the normal host striatum. The coordinates were AP = 1.5 mm, ML = ±2.6 mm from bregma and DV = 5.5 mm from dura (32).

#### *Body Weight*

Body weight was monitored immediately before and after the surgery (for 7 days after transplantation).

#### *Behavioral Tests*

*Spontaneous nocturnal locomotion.* In order to detect any posttransplantation changes in spontaneous locomotor behavior, the topography of nocturnal locomotion was recorded using computerized Digiscan-16 Animal Activity Monitors (Omnitech Electronics, Inc., Columbus, OH). Locomotion measurements consisted of ambulatory measures: horizontal activity (HA), total distance (TD), rest time (RT), movement time (MT), average number of movements (NM), average speed (AP), average distance (AD); rearing measures: vertical activity (VA), number of vertical movements (VM), vertical time (VT); stereotypy measures: stereotypy time (ST), number of stereotypical behaviors (NS), stereotypy count (SC); and directional measures: clockwise (CR) and anticlockwise (AC). These 15 measurements provided a detailed topography of locomotion (36) which has been previously shown to be sensitive to disruption of the striatum (17).

To measure locomotion, the rats were placed individually into the monitors during the dark phase of a 12-hour light/dark cycle (17.00–6.00 hr) for 13 hours with food and water freely available. The locomotor activity was assessed 3, 6, 9, 15 and 20 weeks after transplantation.

#### *Statistics*

The measurements of locomotor activity and body weight were statistically analyzed using two-way Analysis of Variance (ANOVA) for repeated measures. Statistical Analysis System (SAS) General Linear model procedure was used for data processing. Post hoc comparisons were performed and the significance level was adjusted by using the Bonferroni correction.

#### *Histology*

At the end of the behavioral studies, all the transplanted rats were examined histologically 5–11 months after transplantation. To evaluate the viability and histological characteristics of the striatal transplants, sections were stained for Nissl with cresyl violet. The mean sums of the maximum cross-sectional areas for both sides of the transplants were computed by using the Sigma Scan Digitizing system (Jandel Scientific).

### RESULTS

#### *Body Weight*

A significant volume-related weight loss during the period of the first postsurgical days was found in all transplant groups, $F(4,273) = 45.74$, $p<0.0001$. Post hoc comparisons revealed that all transplanted groups, including the SHAM group, significantly differed from the normal controls ($p<0.001$). Across all seven postsurgical days, the 6 μl group lost significantly more weight than both the 3 μl ($p<0.005$) and 1.5 μl ($p<0.001$) groups. Interestingly, the 6 μl SHAM group lost significantly more weight than the 3 μl ($p<0.001$) and 1.5 μl ($p<0.001$) transplant groups, but not significantly different from the 6 μl transplant group ($p<0.066$). The transplant groups and the SHAM-lesioned group returned to their initial body weight by 2–5 days following surgery. The days required for the rats to return to their presurgery body weight were also volume related. It took 4 days for the 6 μl transplant group to return to its initial weight, whereas for the 3 μl and 1.5 μl groups it took only 2 days. The 6 μl SHAM group required 5 days to recover its initial weight.

#### *Spontaneous Locomotion*

Spontaneous nocturnal locomotion was transiently altered following transplantation. As shown in Fig. 1, rearing behavior had changed most; therefore, it was examined over the time course of the experiment as shown in Fig. 2. Significant group effects were

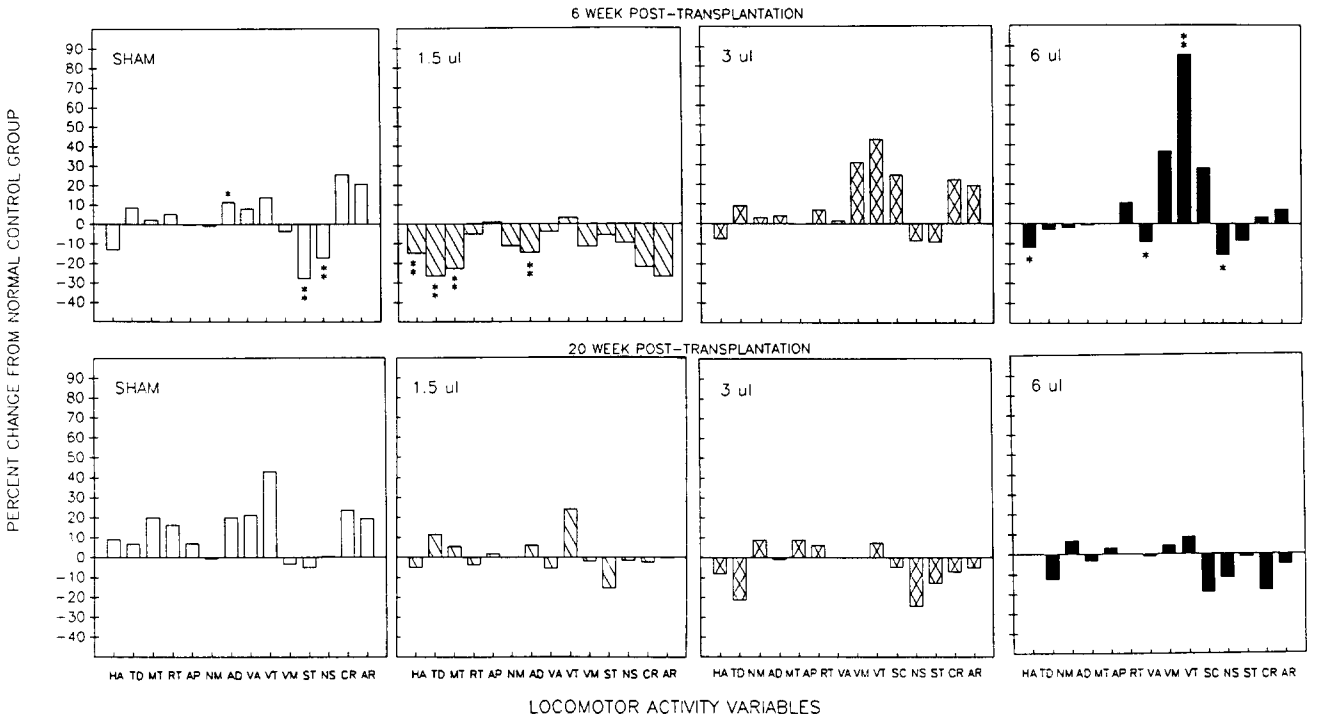


FIG. 1. The effect of bilateral injection of vehicle (SHAM) or 1.5, 3, or 6 μl of fetal striatal tissue on locomotion as measured on Digiscan Animal Activity Monitors at 6 (upper panel) and 20 weeks (lower panel) postsurgery. Data are presented as mean percentages of normal control animals' activity for 10-hour period (20.00–06.00) of 60-min test session. HA: horizontal activity; TD: total distance; NM: number of movements; AD: average distance per move; MT: movement time; AP: average speed; RT: rest time; VA: vertical activity; NV: number of vertical movements; VT: vertical time; SC: stereotypy counts; NS: number of stereotypic behaviors; ST: stereotypy time; CR: number of clockwise movements; AR: number of anticlockwise movements. *$p<0.05$ vs. normal control group, **$p<0.01$ vs. normal control group.

found in rearing activities at the 6th [VT, $F(4,494)=8.43$, $p<0.0001$] and 9th week [VT, $F(4,494)=9.62$, $p<0.0001$; VA, $F(4,494)=6.22$, $p<0.0001$] after transplantation. Post hoc comparisons revealed that, compared to the normal control group, the 6 μl group demonstrated significantly increased rearing activity during the 3- (VT, $p<0.05$) and 6-week periods (VT, $p<0.001$). Decreased ambulation (HA and AD, $p<0.05$, Fig. 1) and decreased stereotypy time (ST, $p<0.05$, Fig. 1) were observed at the 6-week period. The 3 μl group showed significantly increased rearing activity at the 9-week period (VA, $p<0.001$; VT, $p<0.001$; VM, $p<0.05$, Fig. 2) compared to the control group. In contrast, the 1.5 μl transplantation group showed no change in rearing activity and a decrease in ambulation (HA, TD, MT and AD, $p<0.01$) at the 6-week period after the transplantation. The locomotor activity of all transplanted groups returned to approximately control levels by 20 weeks after transplantation (Figs. 1 and 2).

*Histology*

Nissl staining revealed that the striatal transplants survived. Examples of the transplants for each group are showed in Fig. 3. Considerable variation was seen in the overall size of the grafts, with individual values ranging from 0.3 to 7.7 $mm^2$ in cross-sectional areas. As indicated in Table 1, the groups were significantly different in maximum cross-section areas, $F(2,21)=6.34$, $p<0.007$. The post hoc comparisons revealed that the 6 and 3 μl groups had significantly larger maximum cross-sectional areas than that of the 1.5 μl group. The 6 μl group was not significantly

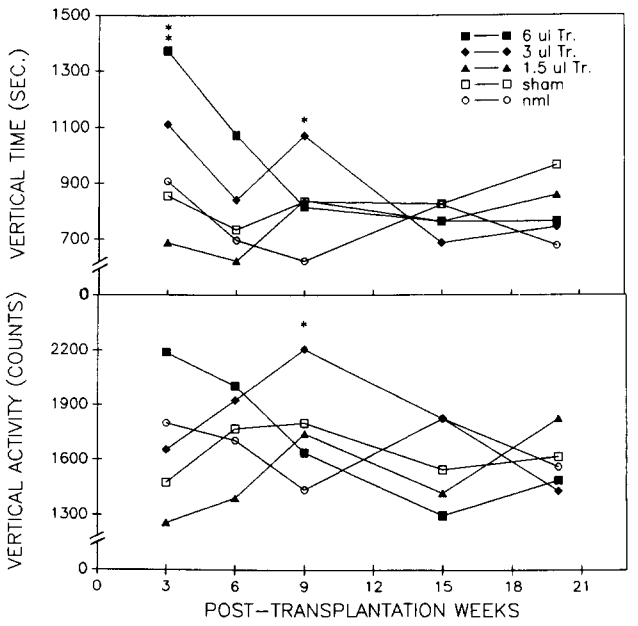


FIG. 2. The effect of bilateral injection of vehicle (SHAM) or 1.5, 3, or 6 μl of fetal striatal tissue on 10 hour (20.00 to 06.00 hr) vertical time (upper panel) and vertical activity counts (lower panel) 3, 6, 9, 15 and 20 weeks following surgery. *$p<0.05$ vs. normal control group, **$p<0.01$ vs. normal control group.

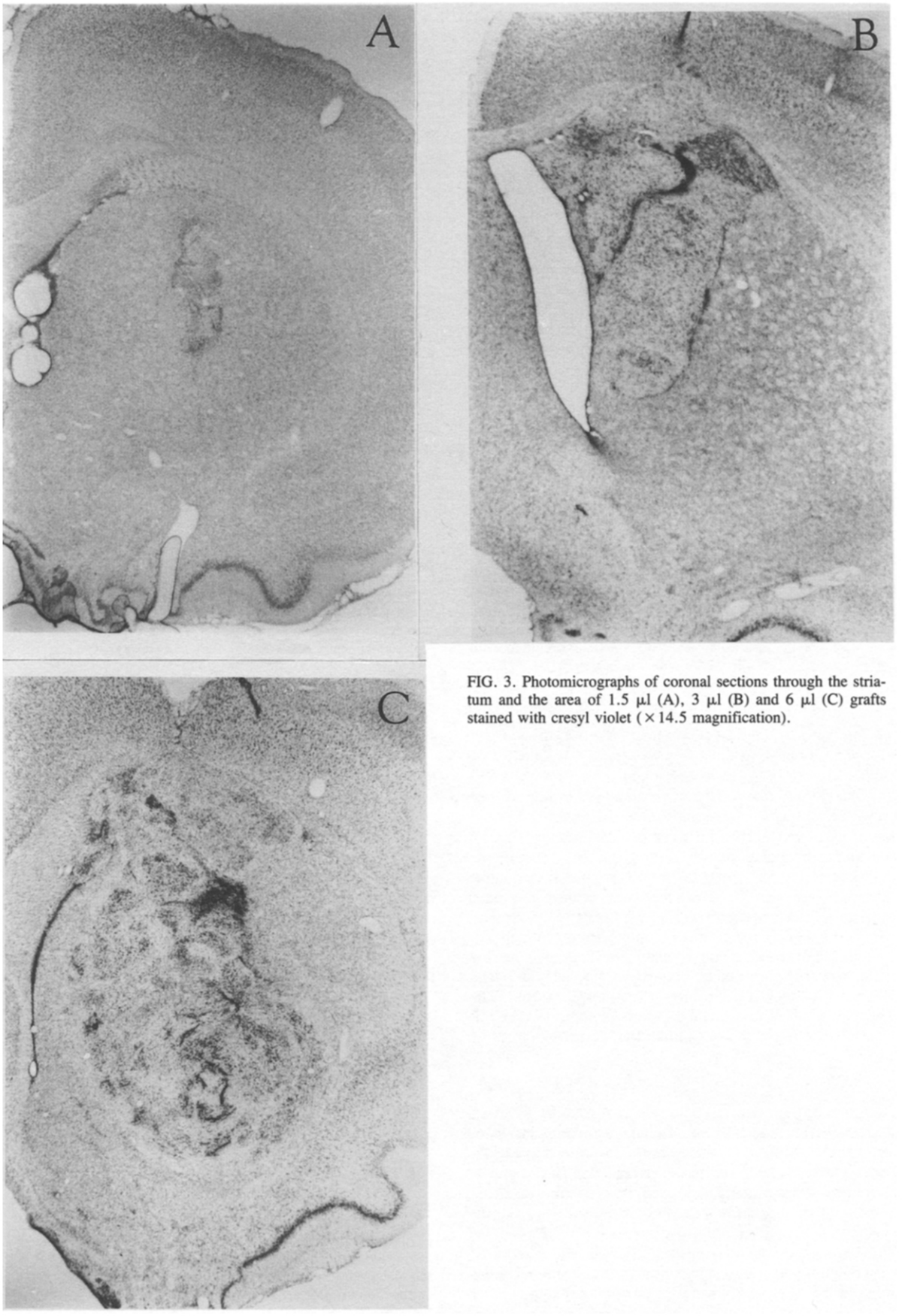


FIG. 3. Photomicrographs of coronal sections through the striatum and the area of 1.5 μl (A), 3 μl (B) and 6 μl (C) grafts stained with cresyl violet (×14.5 magnification).

TABLE 1

THE MEAN SUMS OF THE MAXIMUM CORONAL CROSS-SECTION AREAS FOR BOTH SIDES OF THE TRANSPLANTS AND MEAN ANTERIOR-POSTERIOR EXTENTS IN 6, 3 AND 1.5 μl GROUPS REPRESENTED BY MEANS (S.E.M.)

| Group | n | Sum of Maximum Cross-Section Areas | Mean Anterior-Posterior Extents |
|---|---|---|---|
| 6 μl | 9 | 7.47 ± 0.90* | 1.92 ± 0.23*† |
| 3 μl | 8 | 5.79 ± 1.0* | 1.33 ± 0.15* |
| 1.5 μl | 7 | 3.12 ± 0.46 | 0.86 ± 0.11 |

*Significantly different from the 1.5 μl group, $p<0.05$.
†Significantly different from the 3 μl group, $p<0.05$.
Areas measured by $mm^2$ and anterior-posterior extents measured by mm.

different from the 3 μl group. Furthermore, the groups were also significantly different in the mean anterior-posterior extent of the transplants, $F(2,21)=8.49$. Post hoc comparisons revealed that the 6 μl group had significantly longer anterior-posterior extents than those of the 3 and 1.5 μl groups. The transplants in the 3 μl group extended significantly longer than that of the 1.5 μl group.

The transplants were readily distinguished from the host tissue by their appearance. Glial cells were visible along the boundaries between host and grafts. In some cases the transplants grew along the dorsoventral axis and replaced the overlying cerebral cortex and corpus callosum. The compression of corticofugal fibers bundles (indicated by changed shape from round to oval shapes) was noted in the host striatum adjacent to the large transplants.

## DISCUSSION

The transplantation of fetal striatal tissue into the striatum of normal rats produced alterations in locomotor behavior which were transient and recovered by 20 weeks.

The fetal striatal transplants into normal striatum produced a distinct pattern of initial locomotor changes, i.e., a marked increase in rearing activity in contrast to some smaller changes in ambulation and stereotypy compared with normal controls. This pattern was different from that produced by excitotoxin lesions induced by kainic acid or ibotenic acid which have been shown to produce increases of similar amplitudes in the ambulation, rearing, and stereotypy measures (17). Although the mechanism underlying these changes is unclear, the increase in rearing activity induced by the transplants is strikingly similar to that following dopaminergic stimulation by high doses of d-amphetamine (38).

Our experiment demonstrated that the initial body weight loss induced by transplanting fetal tissue into intact striatum is similar to that of excitotoxic-striatal lesion-induced weight loss, which results from a temporary aphagia and adipsia (34). Since the 6 μl SHAM group also showed the weight loss, the initial weight loss cannot be ascribed to the transplanted fetal striatal tissue, but is related to the injection volume introduced into the striatum.

These results demonstrated that fetal striatal transplant-induced behavioral deficits are related to the initial volumes of the grafted tissue. Transplanted fetal tissue grows to its maximal volume in approximately 6 weeks and then subsequently declines (12). Also, the number of synapses in the transplant reach a maximum value about 6 weeks after transplantation (12). This time frame of transplant development coincides with that of the locomotor perturbations observed in the present experiment, suggesting that transplant growth and development may be related to the observed locomotor alterations.

The histological results suggested that the larger the initial volume of fetal striatal tissue is, the larger the volume of the grafts. Although the 6 and 3 μl groups were not significantly different in the maximum cross-sectional areas, the 6 μl grafts extended further along the anterior-posterior axis. Transplanted fetal tissue grew and expanded within a limited space. The large transplants compressed the surrounding host striatum which may underlie the functional deficits. In support of this, the 6 μl group exhibited an increase in rearing activity 3 and 6 weeks after transplantation. On the other hand, the 3 μl group did not exhibit this increase until 9 weeks posttransplantation. This indicated that the small transplants required time to grow to a volume sufficient enough to cause the increase in rearing behavior.

The behavioral effects of neural transplantation may be manifestations of a dynamic process of interactions between the transplant and the host. The present experiment showed the importance of time in the behavioral perturbation induced by the transplants. The hyperrearing behaviors exhibited by the 6 μl group became apparent as early as 3 weeks after transplantation and returned to normal levels by 9 weeks. The abnormal rearing behavior in the 3 μl group did not become apparent until 9 weeks posttransplantation and dissipated by 15 weeks. By 20 weeks after surgery, the overall locomotor activity in the transplant groups was the same as the normal control group. At present, the cellular mechanisms underlying this recovery are unclear, although it is possible that there is an adaptation and integration between the host and transplant.

# EXPERIMENT 2

As indicated in Experiment 1, abnormal behavior can result from the transplantation of fetal striatal brain tissue into the normal rat striatum. This abnormality is related to the initial volume of transplant, suggesting that the behavioral deficit induced by transplantation is at least a partial result of the physical effects of transplantation (such as expansion and compression). It is not clear whether the specific neurochemical interactions (such as release of neurotransmitter or synaptic contacts) between host and transplant can cause behavioral disturbances. The present experiments examined this issue by studying the behavioral effects of transplants which differed in neuronal populations, intrinsic neurotransmitters, and potential host connections (afferent or efferent) with host striatum. The following experiment examined the effects of transplants from different fetal brain regions on locomotor behavior, drug-induced locomotor behavior, catalepsy, delayed reward alternation, body weight regulation and food and water intake. These behavioral tests have been reported to be sensitive to striatal disruption (9, 22, 34, 41).

## METHOD

### *Subjects*

Adult male Sprague-Dawley rats (n = 53 Zivic Miller), weighing between 250–300 g, were used and housed as described in Experiment 1. Food and water were freely available except during the delayed rewarded alternation testing.

### *Transplantation*

The rats received bilateral transplants of 3 μl of either E14–15 fetal cortex (n = 9) (CTX, mostly frontal and parietal parts of the cortex), substantia nigra (n = 9) (SN, ventral tegmental area) or striatum (n = 9) (STR) into the dorsal striatum [AP = 1.3 mm, ML = ±2.6 mm, DV = −5.5 mm from dura, (32)]. The tissue

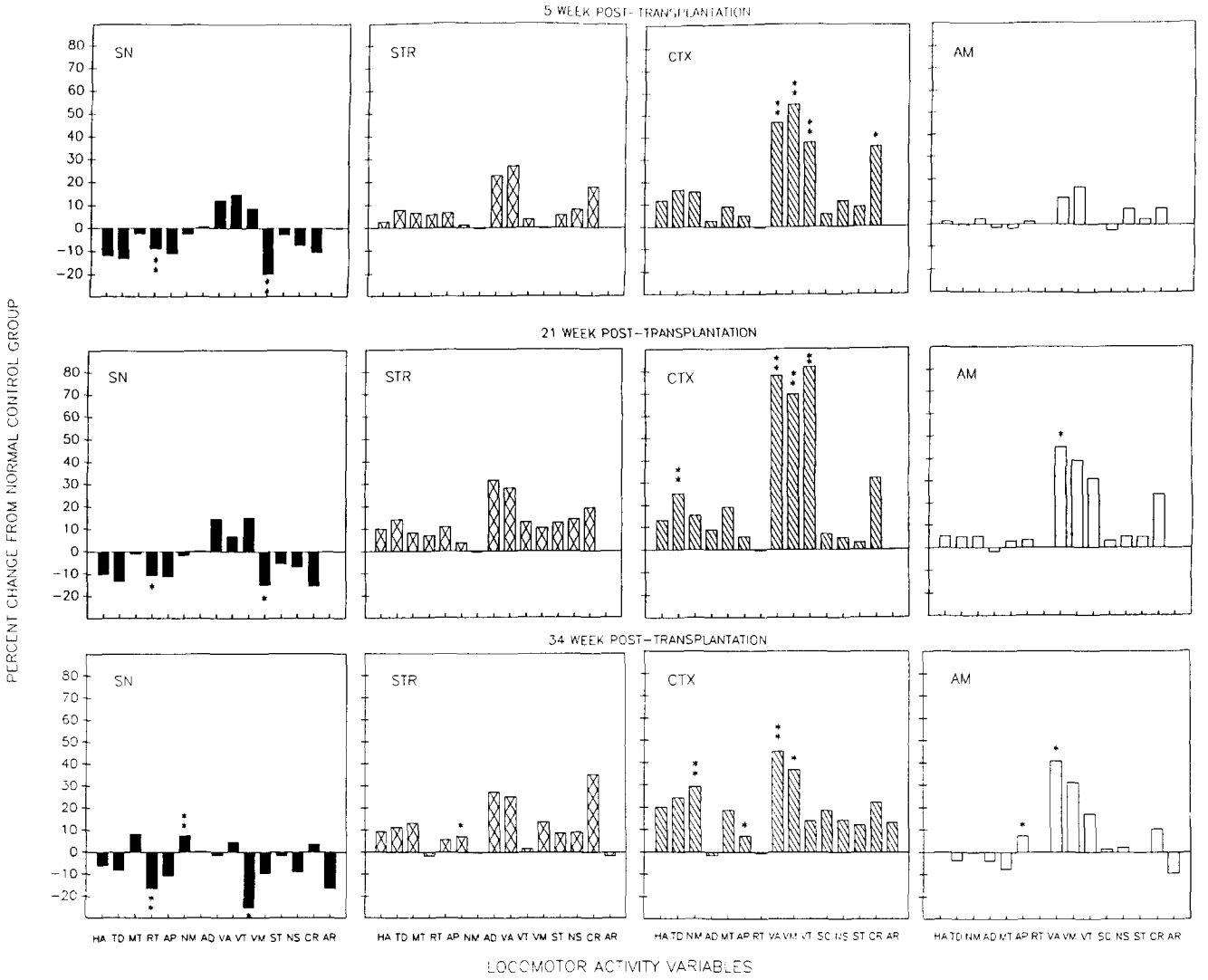


FIG. 4. The effect of bilateral injection of fetal ventral mesencephalic (SN), striatal (STR), cortical (CTX) or adrenal medullary (AM) tissues on locomotion as measured on Digiscan Animal Activity Monitors at 5 (upper panel), 21 (middle panel) and 34 weeks (lower panel) postsurgery. Data are presented as mean percentages of normal control animals' activity for 13-hour period (17.00–06.00) of 60-min test session. The sham group did not show significant change from the normal control group, therefore it is not included. The abbreviations are the same as Fig. 1. *$p<0.05$ vs. normal control group, **$p<0.01$ vs. normal control group.

preparation and transplant procedures were as described in Experiment 1. Another group of rats (n = 9) received adrenal medulla (AM), dissected from 3-week-old rat pups according to the method described by Freed (14). A sham control group (SHAM n = 8) received the (3 μl) equivalent amount of lactated Ringer's solution only. A normal control group (NML n = 9) consisted of unoperated rats.

*Behavioral Testing*

*Spontaneous nocturnal locomotion.* Locomotor activity was recorded using the Digiscan Animal Activity Monitors as described in Experiment 1. Activity was assessed 5, 21 and 34 weeks after transplantation.

*Dopamine agonist-induced locomotion.* Dopaminergic neurotransmission is known to exert a tonic influence on striatal function. Damage to the striatum produced a marked alteration in the response to dopaminergic agonists, such as amphetamine (26–28, 37). In order to detect any possible destruction of striatal function by the transplantation, the following experiments examined the locomotor response of transplanted rats following dopamine agonist administration.

A) Amphetamine (1 mg/kg) was injected intraperitoneally (IP) 6 weeks posttransplantation. At this dose, amphetamine induces locomotor activity (38). Each rat randomly received an injection of either amphetamine (1 mg/kg) or the equivalent volume of saline (1 ml/kg). One week later the order of drug administration was reversed. Postinjection locomotor activity was measured for a 2-hour period.

B) Apomorphine (0.05 mg and 1 mg/kg in 0.01% ascorbic acid solution) or vehicle were injected SC 22 weeks posttransplantation. One mg/kg of apomorphine induces stereotypic behavior as a result of direct stimulation of striatal postsynaptic dopamine receptors (40), whereas 0.05 mg/kg of apomorphine produces a

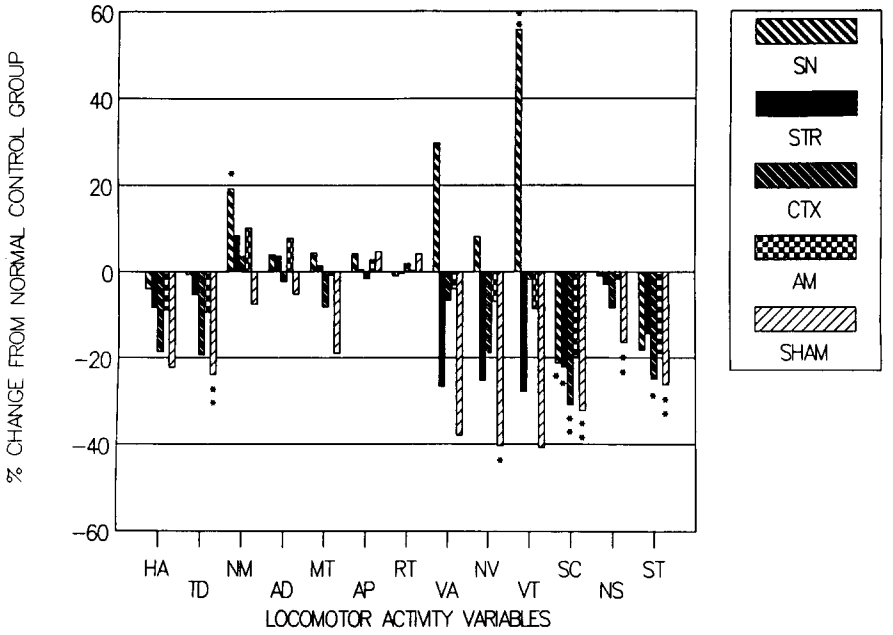


FIG. 5. The effect of amphetamine (1 mg/kg) on locomotion as measured on Digiscan Animal Activity Monitor at 6 weeks following transplantation. The abbreviations are the same as Fig. 1. The data presented as mean percentages of normal controls' activity for the test period of 2 hour. $*p<0.05$ vs. normal control group, $**p<0.01$ vs. normal control group.

sedative effect on locomotor activity, which is presumably mediated by stimulation of presynaptic dopamine receptors, i.e., autoreceptors (39). Using a crossover design each rat was randomly assigned to receive one of the two doses or vehicle. There was an interval of at least one week between any two drug injections. Postinjection locomotor activity was recorded for a 1-hour period at 10-minute intervals.

*Delayed reward alternation.* A variety of evidence indicated that the striatum is involved in cognitive functions, such as spatial learning and spatial memory (30). For example, destruction of the striatum following kainic acid or ibotenic acid produced deficits in delayed reward alternation tests in a T-maze (9,22). To evaluate possible deficits in cognitive performance induced by transplantation, rats were tested on a delayed reward alternation task 6 months posttransplantation according to the method of Wikmark *et al.* (46). Briefly, rats were deprived to about 85% of their free-feeding body weight by limiting their daily ration of food. To avoid visual compensation the maze was placed in an environment which lacked visual cues. Animals initially received 3 days (10 minutes each day) of habituation in which each rat was placed into the T-maze with food pellets scattered on the floor, and allowed to explore freely for 10 minutes each day. At the conclusion of habituation, one day of pretraining began, in which rats were repeatedly placed into the starting box, and immediately released until they entered one of the arms within 5 seconds after their release. At the conclusion of pretraining formal training began consisting of 11 trials per session. Due to the large number of rats ($n=53$) being tested (only 27 rats could be tested each day at the beginning), the first 5 formal training sessions were given every other day, the rest of the 15 sessions were given on consecutive days until a total of 20 test sessions were obtained. At each session, on the initial trial both arms were baited. On the remaining 10 trials only the side which was not visited during the previous run was baited. The rats were rewarded with a 150 mg food pellet (P. J. Noyes Company Inc., Lancaster, NH) for entering the correct side. The total number of correct alternations per day were statistically analyzed.

*Catalepsy test.* Catalepsy in laboratory animals is defined as a failure to correct an externally imposed posture. Haloperidol, a dopamine receptor blocker, is a potent cataleptic agent, whose action is mediated via the striatum (41). Excitotoxic lesions of the striatum are known to attenuate haloperidol-induced catalepsy in rats (5,33). In the present experiment, the haloperidol-induced catalepsy tests were conducted at 17 weeks following transplantation according to the method of Sanberg *et al.* (35). Each rat was gently placed with its forepaws on a horizontal bar (1 cm in diameter) positioned 12 cm above the floor. Catalepsy was measured as the time (in seconds) spent in this position until both forepaws were placed on the floor. Each rat was tested for a maximum 600 seconds. This procedure was run for each rat 2 hours after the administration of either saline or haloperidol. Animals were randomly selected using a crossover design to receive one of the three drug solutions: saline, or haloperidol 1 or 2 mg/kg. The interval between any two injections was 5 days.

*Food and water intake.* At 24 weeks after transplantation, 24-hour food and water intake was measured under ad lib conditions, and also following a 24-hour food or water deprivation period.

*Body weight.* Body weight was monitored every month throughout the study.

### *Statistical Analysis*

The same statistical methods were used as in Experiment 1 for spontaneous locomotion, the delayed rewarded alternation and body weight tests. A three-way ANOVA for repeated measures was used for drug-induced locomotion. A one-way ANOVA was used for both catalepsy test and food and water intake measurements.

### *Histology*

At the end of the behavioral studies, all the transplanted rats

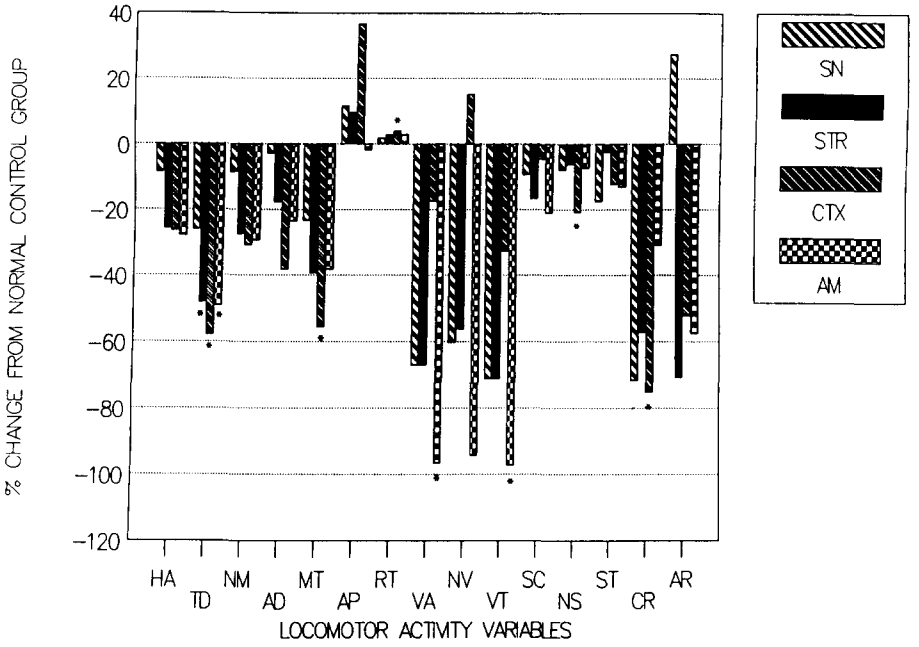


FIG. 6. The effect of apomorphine (1 mg/kg) on locomotion as measured on Digiscan Animal Activity Monitor at 22 weeks following transplantation. The sham group did not show significant change from the normal control group, therefore it is not included. The abbreviations are the same as Fig. 1. The data presented as mean percentages of normal controls' activity for the test period of 1 hour. $*p<0.05$ vs. normal control group, $**p<0.01$ vs. normal control group.

were examined histologically 9–15 months after transplantation. To evaluate the viability and histological characteristics of the transplants, sections were stained for acetylcholinesterase (AChE). The mean sums of the maximum cross-sectional areas for both sides of the transplants were computed as described in Experiment 1.

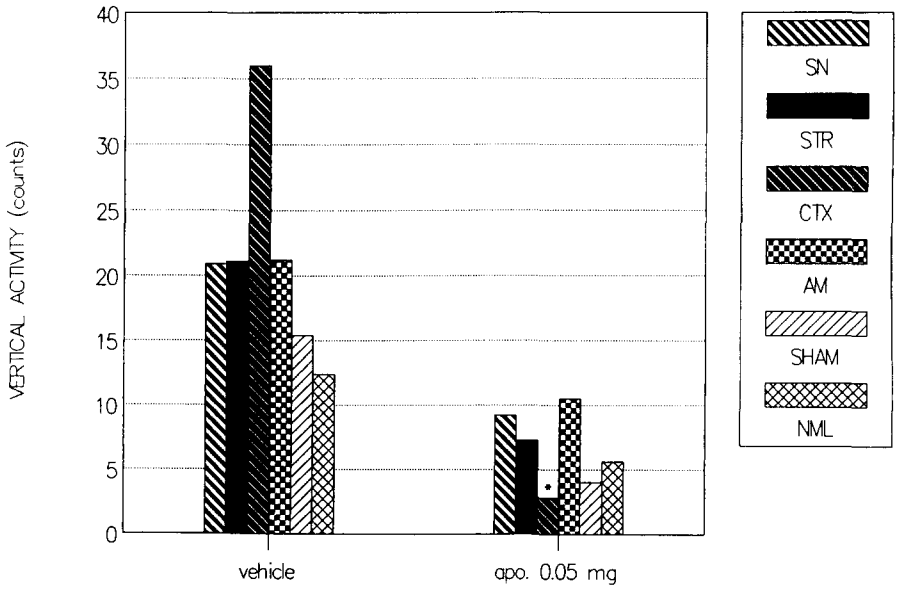


FIG. 7. Apomorphine (0.05 mg/kg) and vehicle injection (0.01% ascorbic acid solution) induced mean vertical activity during 1 hour postinjection test. Post hoc comparison revealed significant reduction in vertical activity in the CTX group ($p<0.05$) compared to its activity induced by the vehicle injection.

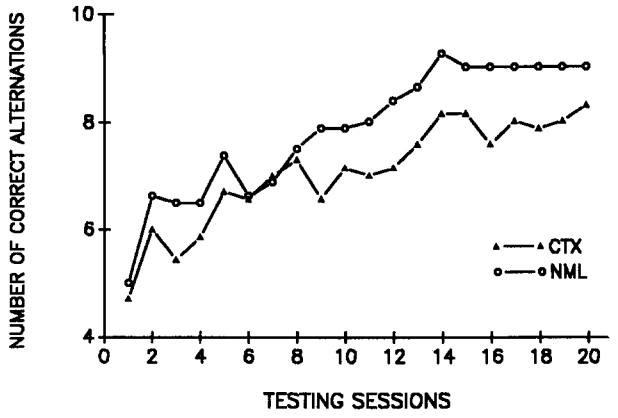


FIG. 8. Delayed rewarded alternation. These data present the mean number of correct alternations of daily test session of 10 trials. Two-way ANOVA for repeated measures revealed that the CTX group had significantly reduced the number of correct alternations ($p<0.05$) compared to the control group. CTX: cortex transplant group; NML: normal control group.

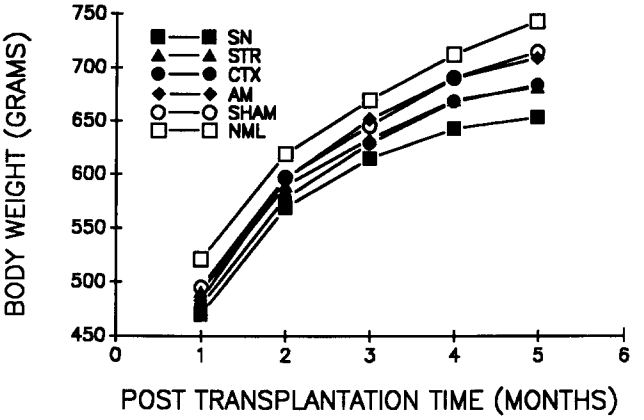


FIG. 10. Body weight. These data present the mean monthly measured body weight. Post hoc comparisons revealed that the SN group had a significant body weight reduction compared with the normal control group ($p<0.05$).

RESULTS

*Spontaneous Nocturnal Locomotion*

Fetal tissue transplantation produced changes in locomotor activity which were similar in extent to those observed in Experiment 1. The groups were significantly different in rearing activities at 5 weeks [VT, $F(5,611)=5.57$, $p<0.0001$; VA, $F(5,611)=6.23$, $p<0.0001$; VM, $F(5,611)=7.91$, $p<0.0001$], 21 weeks [VT, $F(5,611)=8.21$, $p<0.0001$; VM, $F(5,611)=7.54$, $p<0.0001$] and 34 weeks [VT, $F(5,611)=3.80$, $p<0.002$; VM, $F(5,611)=4.52$, $p<0.0005$; VA, $F(5,611)=5.46$, $p<0.0001$]. Post hoc comparisons revealed that the greatest changes were observed in the CTX transplant group. This group had significantly elevated rearing activity compared to the normal controls (VA, VT and NV, $p<0.01$, see Fig. 4) which persisted throughout the tests at 5, 21 and 34 weeks posttransplantation testings (Fig. 4). The AM group also had significantly increased vertical activity ($p<0.05$, 21 and 34 weeks, Fig. 4) when compared to the normal control group, but this developed later at weeks 21 and 34. By 34 weeks after transplantation, the increased rearing behavior observed in the CTX group during the 5th and 21st week either returned to normal control levels (vertical time) or was reduced significantly (vertical activity and vertical movement, Fig. 4).

Significant group differences in ambulation and stereotypy activities were also observed at 5 weeks [AD, $F(5,611)=6.47$, $p<0.0001$; SC, $F(5,611)=5.27$, $p<0.0001$], 21 weeks [TD,

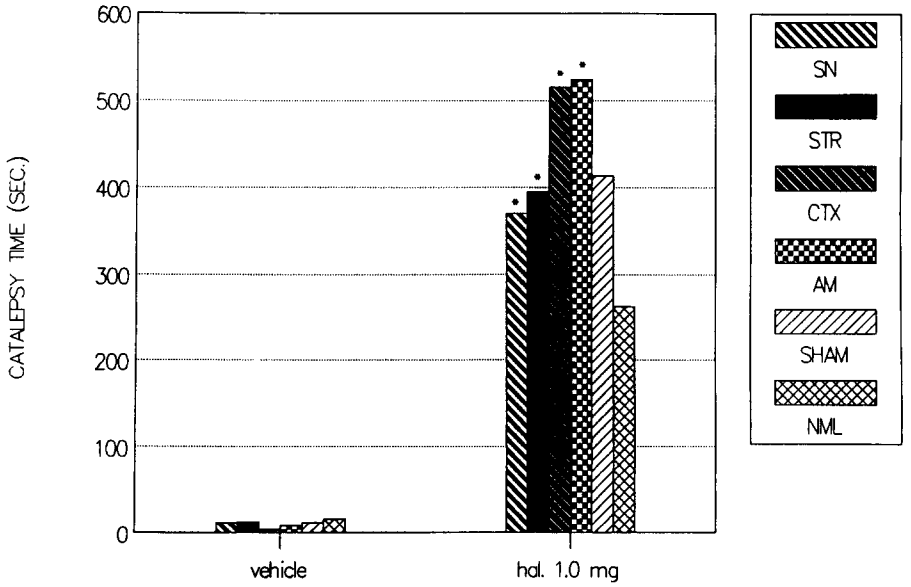


FIG. 9. Mean catalepsy time (sec) induced by haloperidol (1 mg/kg) and saline 2 hours following the injection. Asterisks indicate the significant changes from the normal control group in post hoc comparisons (*$p<0.05$).

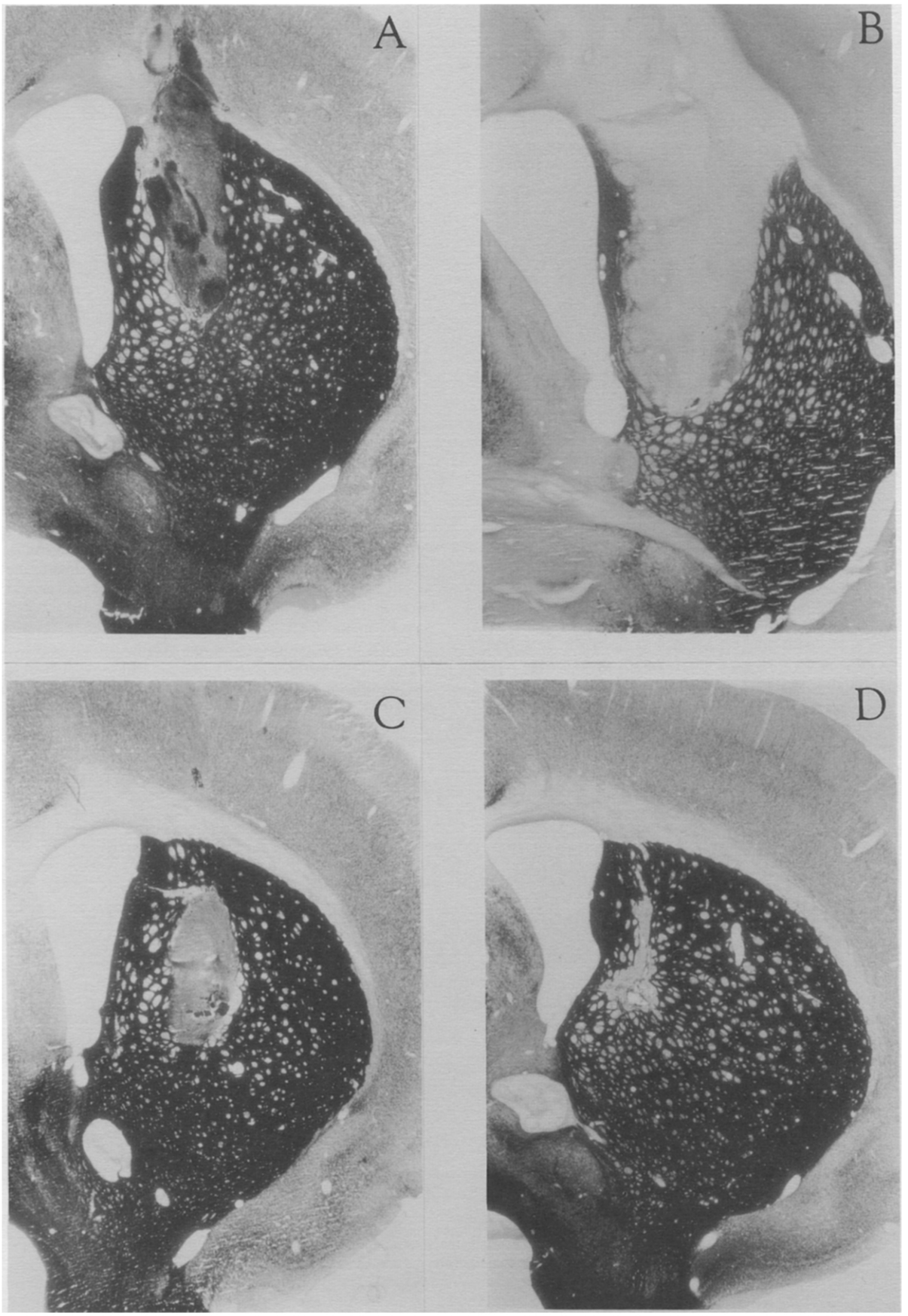
A
B
C
D

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FIG. 11. Photomicrographs of acetylcholinesterase-stained coronal sections through the striatum and the area of striatal graft (A), cortex graft (B), substantia nigra graft (C) and adrenal medulla graft (D) (× 14.5 magnification).

$F(5,611)=5.44, p<0.0001$; AS, $F(5,611)=5.04, p<0.0002$; AD, $F(5,611)=10.88, p<0.0001$] and 34 weeks [NM, $F(5,611)=4.87, p<0.0002$; AD, $F(5,611)=5.82, p<0.0001$; AP, $F(5,611)=3.62, p<0.003$; SC, $F(5,611)=6.27, p<0.0008$]. Post hoc comparisons revealed that compared to the controls, the CTX group showed increased activity in total distance (TD, $p<0.05$, 21 weeks), number of movements (NM, $p<0.01$, 34 weeks), and average speed (AP, $p<0.05$, 21 and 34 weeks) (Fig. 4). In contrast to the hyperactivity of the CTX group, the SN group showed persistent hypoactivity in AD ($p<0.01$, 5, 21 and 34 weeks, Fig. 4) and in SC ($p<0.05$, 5 and 21 weeks, Fig. 4) when compared to the normal control group. In other ambulatory measurements, such as HA and TD, the SN group was not different from the normal control group; however, it was significantly different from the CTX and STR transplanted groups (see Fig. 4).

The STR group (homotopic transplant group) and the SHAM group showed no significant changes compared to the normal control group, except that in the week 34 test, like other transplant groups, they moved at a significantly higher speed than the normal control group (SN and SHAM, $p<0.01$; STR, CTX and AM, $p<0.05$, Fig. 4).

*Dopamine Agonist-Induced Locomotion*

*Amphetamine-induced locomotion.* All groups showed significantly increased locomotor activities following amphetamine (1 mg/kg). The significant group differences were shown in the following measurements: TD, $F(5,752)=2.44$, $p<0.05$; NM, $F(5,752)=3.82$, $p<0.01$; VA, $F(5,752)=4.08$, $p<0.0012$; NV, $F(5,752)=2.97$, $p<0.011$; VT, $F(5,752)=6.85$, $p<0.0001$; SC, $F(5,752)=4.08$, $p<0.0012$; NS, $F(5,752)=4.03$, $p<0.0012$; and ST, $F(5,752)=2.24$, $p<0.05$. Post hoc comparisons showed that compared to the normal control group the SN, STR, CTX and SHAM groups were significantly lower in SC (SN and STR, $p<0.05$; CTX and SHAM, $p<0.01$, Fig. 5) and CTX and SHAM groups were also lower in ST (CTX, $p<0.05$; SHAM, $p<0.01$, Fig. 5). Furthermore, the SHAM group showed decreased HA ($p<0.01$), VM ($p<0.05$), NS ($p<0.01$) and AR ($p<0.01$). Unlike the response of all the other transplant groups which had demonstrated a degree of lower activity in both ambulation and rearing measures, the SN group showed a significant increase in NM ($p<0.05$) and VT ($p<0.01$, Fig. 5) compared to the normal control group.

*Apomorphine-induced locomotion.* Following apomorphine (1 mg/kg) injections, all transplant groups were hypoactive relative to the normal control group (Fig. 6). For example, the CTX, STR and AM groups travelled significantly less distance than the normal control group ($p<0.05$, Fig. 6). The CTX group had significantly reduced MT ($p<0.05$, Fig. 6) and CR ($p<0.05$, Fig. 6). In addition, the AM group showed significantly reduced rearing activity in VA and VT ($p<0.05$, Fig. 6). There was no difference between the control group and the transplant groups in the apomorphine (1 mg/kg)-induced stereotypic measures (SC, NS and ST, Fig. 6), except the CTX group which significantly reduced NS ($p<0.05$, Fig. 6). Following injection of 0.05 mg/kg apomorphine at which the presynaptic autoreceptors are normally activated (39), the CTX group exhibited significant reduction in its locomotion ($p<0.05$) as much as seven-fold compared to its own locomotor activity after vehicle injection (Fig. 7).

*Delayed Reward Alternation*

The CTX group made significantly ($p<0.05$) fewer correct choices in the delayed rewarded alternation test [group effect, $F(5,39)=3.05$, $p<0.02$]. After 20 sessions with a total of 200 trials for each rat, three rats from the CTX group still did not reach the criteria of 90% correct alternation for three consecutive days. The other groups did not differ from the controls (Fig. 8).

*Catalepsy*

The catalepsy scores were significantly different among the groups at 2 hours, $F(5,43)=3.18$, $p<0.015$, following 1 mg/kg haloperidol injection. Post hoc comparisons revealed that all the transplant groups except the SHAM group had significantly higher catalepsy scores compared to the normal control group (Fig. 9).

*Body Weight*

Although all transplant groups including the SHAM transplant group showed trends of reduced body weight [the group effect, $F(5,259)=2.71$, $p<0.02$], post hoc comparisons revealed that only the SN group was significantly different from that of the control group ($p<0.05$, Fig. 10).

*Food and Water Intake*

Abnormal food and water intake was only observed in the SN group. During a 24-hour food intake testing, the SN group ate significantly less food compared with the control groups, $t(24)=2.49$, $p<0.05$. During the 24-hour feeding period following 24 hours of food or water deprivation, the SN group drank significantly less water than the normal control group, $t(24)=2.16$, $p<0.05$ and $t(24)=2.78$, $p<0.01$.

*Histology*

AChE staining within the striatal transplants was patchy and contained AChE positive neurons and fibers (Fig. 11A). Cortical transplants exhibited many AChE terminals with similar appearance to that of the host cortex (Fig. 11B). Nigra transplants

TABLE 2

THE MEAN SUMS OF THE MAXIMUM CORONAL CROSS-SECTION AREAS FOR BOTH SIDES OF THE TRANSPLANTS IN THE SN, STR, CTX AND AM GROUPS REPRESENTED BY MEANS (S.E.M.)

| Group | n | Sum of Maximum Cross-Section Areas |
|---|---|---|
| SN | 7 | 4.14 ± 0.46*† |
| STR | 7 | 3.24 ± 0.55*† |
| CTX | 7 | 14.24 ± 2.50† |
| AM | 7 | 0.44 ± 0.15* |

*Significantly different from the CTX group, $p<0.01$.
†Significantly different from the AM group, $p<0.01$.
Areas measured by $mm^2$.

showed light staining (Fig. 11C) and adrenal medulla transplants showed a lack of AChE staining (Fig. 11D). Transplants were easily identified by their patchy (STR) or lack of AChE staining (CTX, SN and AM) in contrast with the host striatum. Lack of corticofugal fiber bundles also characterized the transplants. Most of the transplants were located in the parenchyma of host striatum. In some cases the transplants grew along the dorsoventral axis and replaced the overlying cerebral cortex. There were two cases in each of the CTX, STR and SN groups, in which a transplant was found in the lateral ventricle. This might have been due to the fetal tissue being surgically delivered into or close to the lateral ventricle, or that the transplants later grew into lateral ventricle. As indicated in Table 2, the groups were significantly different in their maximum cross-sectional areas for both sides of the transplants, $F(3,24)=21.32$, $p<0.00001$. The post hoc comparisons revealed that the CTX group had significantly larger maximum cross-sectional areas than that of the STR ($p<0.0013$), SN ($p<0.0022$) and AM ($p<0.0003$) groups. The STR ($p<0.0006$) and SN ($p<0.000$) groups had larger cross-sectional areas than that of the AM groups. The STR group was not different from the SN group in cross-sectional area. As in Experiment 1, compressed corticofugal fiber bundles were seen in the host striatal tissue adjacent to larger grafts.

## DISCUSSION

These experiments clearly indicated that the transplantation of different areas of the fetal brain into an intact striatum resulted in different behavioral deficits. For example, in contrast with the other transplant groups, the SN group showed a persistent lower level of locomotion. Moreover, following 1 mg/kg amphetamine, the SN group demonstrated a marked increase in the number of movements and vertical time, whereas other transplant groups showed significantly fewer increases than the normal control group. Finally, unlike the other groups, the SN group had significantly reduced food and water intake after 24-hour food or water deprivation, resulting in significant body weight loss.

These behavioral changes unique to the SN group suggested that specific interactions might have taken place between the substantia nigra transplant and the host striatum. Ventral mesencephalic grafts transplanted into the striatum have been reported to contain tyrosine hydroxylase positive neurons with extensive fibers growing into and forming synaptic contacts with the host striatum (2, 15, 16, 25). Evidence from intracerebral dialysis studies (47) of ventral mesencephalic grafts in dopamine-depleted striatum revealed that the transplants can spontaneously release dopamine and increase dopamine release in response to the administration of amphetamine (43). Thus, it is possible that there is an ectopic dopaminergic influence that interferes with striatal function causing behavioral perturbation. The increased rearing exhibited by the SN group following amphetamine supports the contention that an additional graft-derived pool of dopamine is available.

The spontaneous locomotor alteration of the SN group was a persistent decrease in activity. This may seem contradictory, since excess dopamine usually would produce increased locomotor activity. However, this may be related to secondary changes resulting from the excessive dopaminergic influence. For instance, tonically released dopamine from the nigra transplant may diffuse through synapses into the surrounding striatal host tissue resulting in a down regulation of the postsynaptic dopamine receptors which in turn reduce the effectiveness of the existing dopamine transmission. The functional endpoint of this down regulation may be a tonic decrease in locomotor activity. Alternatively, dopamine released from the terminals derived from the nigra transplants may activate dopamine autoreceptors on host DA terminals and decrease dopamine release in the host dopamine afferent neurons.

The different behavioral perturbations demonstrated in the SN groups are consistent with a possible dopamine interaction with the host striatum. However, the contribution of other neuronal elements in the transplant cannot be excluded. The ventral mesencephalic tissue is not pure substantia nigra but contains a variety of other neuronal populations. Immunocytochemical data revealed that the ventral mesencephalic transplants contained TH, serotonin (5HT) and dopamine-β-hydroxylase (DBH)-positive neurons (24). Although the behavioral influence of 5HT- and DBH-containing neurons in the transplant was not clear, the possibility that these and other elements influence the behavioral perturbations cannot be excluded.

Both substantia nigra and adrenal medulla (AM) transplantation have been developed as potential therapies for Parkinson's disease. Little is known, however, about the behavioral deficits they may produce. In contrast to the SN group, the AM group demonstrated an increase in spontaneous rearing activity without an altered responsiveness to amphetamine and no regulatory deficits. These differences may be due to 1) differences in neurotransmitter content between SN and AM grafts. The SN transplant contains mainly dopamine, some serotonin and norepinephrine (24), whereas AM graft contains the largest proportion of epinephrine and to a lesser extent norepinephrine and dopamine (20, 44, 45) or 2) differences in fiber outgrowth from the transplanted tissues. The fibers from SN transplants are capable of growing into and forming synaptic connections within the host striatum, and releasing dopamine and other neurotransmitters. In contrast, AM transplants produce few fibers and very little or no innervation of the host striatum, but secrete catecholamines that may influence the striatum through passive diffusion into the receptor sites (14,20).

The CTX group showed the most severe behavioral change both in the number of locomotor variables affected and in the degree of these deficits. These animals were also impaired in a delayed reward alternation T-maze test. Fetal cortical tissue has been reported to have a high growth potential when transplanted (6). Moreover, it is known that the cortex has an excitatory input to the striatum (31,18), and that the specific [$^3$H] glutamate uptake into the CTX transplant (a marker of a major set of cortical efferent neurons) is the same or even higher than that of normal cortex (23). Both the high growth potential and its related mechanical destruction as well as additional excitatory influence in the striatum may contribute to these disturbances.

The fact that the striatal transplant (homotopic) caused relatively less perturbation than other tissue types may reflect its similar cellular and neurochemical composition to that of the host tissue, which results in better integration and adaptation. The SHAM group did not show strong locomotor perturbations, but when given dopamine agonists, did show some abnormalities, suggesting that the injection of vehicle alone causes behaviorally significant brain damage.

The transplants into intact striatum also produced some alternations in response to the dopamine receptor agonists, apomorphine and amphetamine, and the dopamine receptor antagonist, haloperidol, indicating a disruption of dopamine receptor-mediated functions.

The data from the present study are consistent with Deckel *et al.*'s (8, 10, 11) and Hagenmeyer-Houser *et al.*'s (19) finding that abnormal locomotor behavior can be induced by transplantation of fetal tissue into the intact striatum. However, the present experiments further revealed that these deficits are distinguishable from those induced by excitotoxins. Kainic acid and ibotenic acid produce locomotor hyperactivity with evenly elevated overall locomotor variables including ambulation, rearing and stereotypy (5). On the other hand, the present studies indicated transplants

into the intact striatum caused a dramatic increase in rearing with relatively little or no change in other locomotion dimensions. In addition, the locomotor deficits induced by excitotoxic lesions are relatively permanent, while those induced by transplants are transient. Finally, the general hyporesponsiveness to both d-amphetamine and apomorphine observed in the present experiments following transplantation is dissimilar to the hyperresponsiveness observed in striatal-lesioned rats (9,37). These data suggest that different mechanisms underlie the behavioral deficits induced by excitotoxins and by fetal tissue transplants into the striata of normal rats.

Variations in graft volume and location affected the behavioral outcome of the rats. For instance, the most increased rearing activity was observed in the CTX group which had the largest graft volume among transplant groups. This result is in agreement with Experiment 1, which suggested that the volume of transplant is an important factor affecting behavior. However, the variations of transplant location observed in the present experiment showed no clear correlation with the changes in spontaneous locomotor behavior observed in the transplanted groups. For example, although most of the transplants were located in the parenchyma of the striatum, some of the grafts grew dorsally into cortex and corpus callosum to various degrees. While these results suggested that these variations in the transplant location did not contribute to the increased rearing behavior observed in the CTX and AM group directly, it remains unclear at this point how these variations affected the behaviors.

## GENERAL DISCUSSION

Transplantation of fetal brain tissue into normal adult brain has been used as a probe for developmental and neural plasticity. However, few studies of the behavioral consequences of transplants into the intact brain have been done. Most studies on the behavioral effects of transplantation are performed in environments with neuronal degeneration and denervation created by either mechanical manipulation or neurochemical toxicity. Although these animal models are useful for examining the variability of the transplant, the acute lesion and denervation seen in these models are very different from that produced by the slow neurodegeneration in many human diseases. The normal brain provides an environment that is closely related to the early stages of the disease when most of the neurons are intact, without massive denervation. It is a useful model for studying the neural plasticity, and testing the behavioral effects of brain tissue transplantation for clinical applications.

The future development of transplant therapy should consider its beneficial effects as well as its potential negative consequences. The initial surgical trauma and subsequent interaction with the fetal transplant is likely to cause a series of perturbations in the host. The present study indicated that both mechanical destruction related to transplant volume expansion and neurochemical interferences dependent on tissue type can result in marked disturbances on host functions. Therefore, the transplant volume and its neurochemical "compatibility" should be carefully considered in the development of transplant therapy.

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