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# Excitotoxic Lesions of the Rat Medial Prefrontal Cortex

## Effects on Abnormal Behaviors Associated with Neonatal Hippocampal Damage

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*Neonatal excitotoxic damage of the ventral hippocampus (VH) is a heuristic model of schizophrenia. We investigated whether: (1) neonatal damage of the medial prefrontal cortex (mPFC) has effects similar to the neonatal VH lesion; and (2) intrinsic mPFC neurons contribute to the abnormal behaviors associated with VH lesions. Neonatal rats were lesioned in the mPFC. In adulthood, they showed attenuated locomotion in response to novelty, amphetamine, and MK-801, and enhanced apomorphine-induced stereotypies as compared to controls. Striatal $D_1$ and $D_2$ receptor mRNAs were unaltered. Another group was lesioned in the VH and additionally in the mPFC in adulthood. Destroying mPFC neurons normalized hyperlocomotion to novelty and amphetamine of the neonatally VH lesioned rats. Thus, neonatal damage of the mPFC does not provide a heuristic model of schizophrenia-like phenomena, in contrast to analogous damage of the VH. However, mPFC intrinsic neurons that have developed in the context of abnormal hippocampal connectivity may be responsible for abnormal behaviors in the neonatally VH lesioned rats.* ***[Neuropsychopharmacology 19:451–464, 1998]*** *Published by Elsevier Science Inc.*

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Structural neurodevelopmental abnormalities in the temporolimbic cortex, dysfunction of the prefrontal cortex (PFC), and dysregulation of dopamine and glutamate systems are implicated in the pathophysiology of schizophrenia (Weinberger 1987; Robbins 1990; Grace 1991; Mittleman et al. 1993; Weinberger and Lipska 1995). In an attempt to recreate these neuropathological features in an animal, we previously investigated the consequences of neonatal excitotoxic damage of the ventral hippocampal formation in the rat on behaviors related to dopamine and glutamate function (Lipska et al. 1993, 1995a; Lipska and Weinberger 1993, 1994; Al-Amin et al. 1997). The results of these studies indicate that the neonatally lesioned rats display a constellation of behavioral abnormalities indicative of hyperdopaminergic subcortical activity and hyperresponsivity to glutamate antagonists and that the appearance of these behaviors is delayed until early adult life. Our results and subsequent reports from other laboratories (Flores et al. 1996a; Black et al. 1996; Wan et al. 1996; Wan and Corbett 1997) suggest that this lesion reproduces a constellation of core phenomena associated with schizophrenia, and may thus be used as an animal model of this disorder. Such neonatally lesioned rats also express

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behaviors that implicate dysfunction of the PFC (Chambers et al. 1996; Sams-Dodd et al. 1997), possibly because neonatal damage of the ventral hippocampus disrupts neuronal development of the PFC, with which the hippocampus is closely interconnected (Swanson 1981; Ferino et al. 1987; Jay et al. 1989; Laroche et al. 1990; Jay et al. 1992; Carr and Sesack 1996). Because PFC dysfunction has been shown in rodents (Adler 1961; Lynch et al. 1969; Iversen 1971; Pycock et al. 1980; Kolb 1984; Reibaud et al. 1984; Louilot et al. 1989; Jaskiw et al. 1991; Vezina et al. 1991; Deutch 1992; Jaskiw and Weinberger 1992; King and Finlay 1995; Taber et al. 1995; Karreman and Moghaddam 1996) and in primates (Kolachana et al. 1995; Roberts et al. 1994) to affect subcortical dopamine activity, the effect of the VH lesion on dopamine function might be indirectly mediated by an alteration at the level of the mPFC.

The current study addresses the question of whether direct excitotoxic damage of the prefrontal cortex induced in neonatal rats affects glutamatergic and subcortical dopaminergic function in a manner similar to that observed in animals with the neonatal ventral hippocampal lesion. The lesion was intended to involve the area of the mPFC that receives direct projections from the hippocampus; that is, the prelimbic/infralimbic subregion (Swanson 1981; Jay et al. 1989; Jay and Witter 1991, Ferino et al. 1987; Laroche et al. 1990). Our results indicate that direct neonatal excitotoxic damage of the mPFC does not result in hyperlocomotor activity in response to amphetamine, stress of novelty, or MK-801, as does neonatal damage of the ventral hippocampus (Al-Amin et al. 1997; Lipska et al. 1993). As the second part of this study, we tested if intrinsic mPFC neurons are necessary effectors of the behavioral abnormalities associated with the neonatal (PD7) VH damage. For this investigation, we de-efferented the mPFC in adult rats that had previously undergone neonatal damage of the ventral hippocampus. These data suggest that intrinsic mPFC neurons may, indeed, be responsible for the behavioral changes observed in postpubertal rats with the neonatal lesion of the ventral hippocampus.

## MATERIALS AND METHODS

All animal handling, testing, and surgical procedures were carried out in accordance with NIH Animal Care guidelines.

## NEONATAL LESION OF THE mPFC

### Surgery

Pregnant Sprague–Dawley rats obtained at 14 days of gestation (Taconic) were housed individually in breeding cages with a 12-hour light/dark cycle and fed ad libitum. Male pups (weight 9–13 g, total $n = 83$) within each litter were randomized to sham or lesion status and anesthetized by hypothermia (placing on ice for 10–20 min). The pups were then immobilized by taping on a Styrofoam platform that was positioned in ear bars of the Kopf stereotaxic frame. An incision was made in the skin overlying the skull, and a Hamilton needle was inserted through the skull bilaterally into the medial prefrontal cortex (coordinates relative to bregma: AP +2.5 mm, ML ±0.4 mm, VD −2.3 mm from dura). Ibotenic acid (Sigma, 3 μg in 0.3 μl) in the lesioned rats ($n = 42$) or artificial cerebrospinal fluid (pH = 7.4) in the sham-operated animals ($n = 41$), was infused at a rate of 0.15 μl/min using an infusion pump. The cannulae were withdrawn 3 minutes after the completion of the infusions, and the incision was closed using Autoclip wound clips (Clay-Adams, Parsippany, NJ, USA). After the procedure, all the pups were placed under a warming lamp and then returned to their mothers. On PD25, all rats were weaned, separated by lesion status, and grouped three or four to a cage.

### Behavioral Testing

***Experiment 1.*** Locomotor activity (distance traveled in cm) of a subgroup of the neonatally operated rats (sham, $n = 10$; lesion, $n = 11$) was tested in photocell monitors (model RXYZCM, Omnitech) at PD35 and PD56. Rats were habituated to the monitors for 60 min, then injected with saline (1 ml/kg, IP) and monitored for 60 min, and finally given amphetamine (1.5 mg/kg, IP), and monitored for an additional 90 minutes. In addition, stereotypy counts (the number of repetitive breaks of the same sets of beams that occur during the period of stereotypic activity) and number of stereotypies (the number of times that the monitor observed stereotypic behavior) were recorded. The same rats were tested at PD35 and PD56.

***Experiment 2.*** Another group of rats (sham, $n = 8$; lesion, $n = 8$), which was not tested before, was used to visually assess stereotyped behaviors at PD35 and PD56. After 60 min habituation in photocell monitors equipped with wire grid bottoms, the rats were injected with apomorphine (0.75 mg/kg, SC). Starting 5 min after the injection, each rat was observed for 15 s at 5 min intervals during the 60-min period. Sniffing, licking, and biting were scored during each interval. The intensity of stereotypic behaviors was scored as follows: 1, fixed sniffing (directed at the floor); 2, short occurrence; 3, occasional bursts; 4, intermittent intense performance; 5, continuous intense performance of either licking or biting (oral stereotypies).

***Experiment 3.*** A new testing-naive group of rats received MK-801, an NMDA antagonist, (sham, $n = 23$;

lesion, $n = 23$). At PD56, these rats were placed in the photocell monitors for a 30 min habituation period, and then they were randomly assigned to receive either saline or one of three doses of MK-801 (0.05, 0.1, or 0.2 mg/kg, SC), and were monitored for another 120 min.

After behavioral testing, all the rats were killed; brains were removed and frozen. Twenty μm sections were cut and Nissl-stained for histological analysis of the lesion.

### In Situ mRNA Hybridization

Rats used for the measurements of apomorphine-induced stereotypy in Experiment 2 (sham, $n = 8$; lesion, $n = 8$) were killed 3 months after the second behavioral testing (PD133). Brains were removed, rapidly frozen in isopentane, and sectioned into 20 μm slices. Striatal slices were used for in situ hybridization histochemistry of $D_1$ and $D_2$ receptor mRNAs.

The probe for the $D_1$ receptor mRNA was a mixture of three 48-mers oligonucleotides complementary to nucleotides 13–60, 520–567 and 664–711 of the rat $D_1$ receptor cDNA (DuPont NEN Research Products). The oligonucleotides were 3′ labeled with [$^{35}$S]dATP using terminal transferase, and then purified by phenol/chloroform extraction followed by precipitation with ethanol. The sections were fixed in 4% formaldehyde, acetylated with acetic anhydride, defatted in chloroform, and dehydrated in a set of graded ethanol solutions. In situ hybridization was performed overnight in humidified chambers at 37°C with the [$^{35}$S[-labeled probe $3.6 \times 10^5$ dpm in 25 μl per section) added to the hybridization buffer (50% formamide, 80 mm Tris-HCl, pH = 7.5, 600 mm NaCl. 4 mm EDTA, 0.1% NaPyrophosphate, 0.2 mg/ml sodium heparin, 10% Dextran $SO_4$, 0.2% SDS, 100 mm DTT). The sections were then washed four times for 15 min each in 1 × SSC at 60°C, two times 30 min each in 1 × SSC at room temperature, rinsed in ethanol, and air-dried. The sections and the $^{14}$C standards were apposed to BioMax Kodak film for 6 days.

To produce an antisense ribonucleotide probe for $D_2$ receptor mRNA, a 347 base–pair-containing clone (a gift from Dr. Kalpana Merchant, Pharmacia & Upjohn Inc., Kalamazoo, MI, USA) was linearized with Xho I restriction enzyme; 0.2 ng (1 μl) of linearized plasmid was labeled using 150 μCi of [$^{35}$S]dUTP and T7 RNA polymerase (for a sense probe Pst I enzyme and T3 polymerase were used). The total volume of this reaction was 10 μl (1 μl each of 10 mm rATP, rCTP, rGTP, 2 μl of 5× transcription buffer, 1 μl of 100 mm dithiothreitol DTT, 1 μl of RNasin, and DEPC water). After incubation for 15 min at 37°C, labeled RNA was precipitated with ethanol in the presence of tRNA and ammonium acetate. After extraction with phenol/chloroform and precipitation with ethanol, the probe (specific activity $3.5 \times 10^9$ dpm/μg) was resuspended in DEPC water, and added to the hybridization buffer (1200 nm NaCl. 20 mm Tris-HCl, 0.04% Ficoll, 0.04% BSA, 0.04% PVP, 2 mm EDTA, pH = 8, 0.02% salmon sperm, 0.1% total yeast RNA, 0.01% yeast tRNA, 20% Dextran $SO_4$) to yield the final concentration of 5 ng/ml corresponding to approximately $5 \times 10^5$ dpm/per section (per 25 μl). The sections were fixed in 4% formaldehyde, acetylated using acetic anhydride, dehydrated in ethanol, and defatted in chloroform. In situ hybridization was carried out overnight at 55°C. After removing the coverslips in 2 × SSC, the sections were treated with RNase A (for 30 min at 37°C), washed in RNase A-free buffer for 30 min at 37°C, washed twice in 2 × SSC for 15 min each at room temperature, once in 0.5 × SSC for 60 min at 55°C, twice in 0.1 × SSC for 30 min each at 60°C, and once in 0.1 × SSC for 15 min at room temperature. The sections were then rinsed with 50 to 100% ethanol solutions with ammonium acetate (300 mM), air-dried, and apposed with the $^{14}$C standards to BioMax Kodak film for 6 days.

Densitometric analysis of films was performed blind to the status of the rat using Macintosh-based image analysis software (NIH, Image). Optical densities were assessed for the whole striatal regions as well as subdivisions of the striatum according to Paxinos and Watson (1986) (dorsolateral, dorsomedial, and ventral striatum, nucleus accumbens core and shell) from four sections per rat, and averaged. Densities interpolated along a $^{14}$C standard curve were converted to disintegrations per min/mm squared (dpm/mm$^2$) (24 dpm/mm$^2$ for every μCi/g of $^{14}$C) according to Miller (1991).

## ADULT LESION OF THE mPFC IN RATS WITH NEONATAL HIPPOCAMPAL DAMAGE

A new group of the neonatal (PD7) rats was lesioned with ibotenic acid (3 μg in 0.3 μl) (lesion, $n = 20$) or infused with artificial cerebrospinal fluid (sham, $n = 19$) in the VH (coordinates relative to bregma: AP −3.0 mm, ML ±3.5 mm, VD −5.0 mm) as described previously (Lipska et al. 1993). At PD35, PD56, and PD140, these rats had been tested in the photocell monitors following administration of either saline or MK-801 (0.05–0.2 mg/kg). The results of these experiments are described elsewhere (Al-Amin et al. 1997). Briefly, rats with neonatal lesions of the ventral hippocampus were markedly hyperactive in response to a novel environment (new photocell cages) and MK-801, as compared to the sham controls at PD56 and PD140 (postpuberty), but not at PD35 (prepuberty). At PD154 (2 weeks after the last testing), these rats were assigned in a counterbalanced fashion (equal numbers of rats from each previous treatment group were represented in the new lesion groups) to receive a subsequent sham or ibotenic

acid lesion of the mPFC. The rats under Equithesin anesthesia (3 ml/kg, IP) were immobilized in the stereotaxic Kopf frame with the incisor set at 2.5 mm below the interaural line. Ibotenic acid (5 μg/0.5 μl) (lesion mPFC) or an equal volume of cerebrospinal fluid (sham mPFC) was infused over 2.5 min bilaterally into the mPFC through the 26-gauge stainless steel cannulae using an infusion pump (the coordinates relative to bregma: AP + 3.5, ML ± 0.7, and VD − 3.5 mm from dura). Four groups of animals were thus formed: sham VH/sham mPFC ($n$ = 10); sham VH/lesion mPFC ($n$ = 9); lesion VH/sham mPFC ($n$ = 10); lesion VH/lesion mPFC ($n$ = 10). The rats were allowed to recover for 4 weeks. They were then tested as described in Experiment 1; that is, locomotion was monitored during the habituation period, after saline and after amphetamine injection (1.5 mg/kg, SC).

## STATISTICAL ANALYSIS

The results of locomotor activity in Experiment 1 were analyzed by a three-factor analysis of variance (ANOVA) followed by post-hoc testing (Fischer PLSD) where appropriate. Lesion status (sham or lesion) was used as an independent variable, and age at testing (PD35 or PD56) and testing interval (5 min bins) were used as repeated measures. The stereotypy scores in Experiment 2 were analyzed by a three-factor ANOVA, with lesion status as an independent variable, and age at testing and testing interval (5 min bins) as repeated measures followed by the Fischer PLSD post-hoc test. The data from Experiment 3 were analyzed by two- (habituation period) or three-factor ANOVA (drug administration intervals), with lesion status and drug as independent variables, and time as a repeated measure. The in situ hybridization data were analyzed by a one-way ANOVA (lesion status) for each region separately. The results from the combined mPFC/VH lesion experiment were analyzed by a two-way ANOVA (mPFC and VH lesions as independent factors) followed by the Fischer PLSD post-hoc test.

## RESULTS

Verification of neonatal and adult mPFC lesions using thionin stained sections revealed cell loss and gliosis restricted to the cingulate areas Cg1 (ventral portion), Cg3, and parts of the infralimbic area IL of the mPFC (Zilles and Wree 1995; Paxinos and Watson 1986) (or a ventral portion of the anterior cingulate area Acd and prelimbic PL, and IL areas, respectively, according to Krettek and Price, 1977) in the anterior–posterior coordinates approximately 3.7 to 2.7 mm from bregma, according to the atlas of Paxinos and Watson. Other areas of the frontal cortex adjacent to Cg1, Cg3, and IL were spared, including the frontal area Fr2 (or medial precentral area PrCm) (Figures 1–3). In the neonatally lesioned animals, there was no cavitation in any case, but atrophy and retraction of tissue in the lesioned areas formed a gap in the midline (Figure 2). In the adult lesioned rats, there was minimal cavitation, accompanied by gliosis and retraction of tissue around the injection site (Figure 3). Seven subjects were deleted from further analysis from the neonatal group because of inappropriate location of the lesion or to lack of discernible damage. Thus, the final number of neonatally mPFC lesioned rats included in the analysis was 9, 7, and 19, in experiments 1, 2, and 3, respectively. The ventral hippocampal lesion included areas CA1 to CA4 in the ventral divisions of the hippocampal formation, parts of the dentate gyrus and the subiculum as described previously (Lipska et al. 1993). One subject was deleted from the adult mPFC lesioned group because of improper location of the ventral hippocampal lesion. Sham-operated rats showed no damage.

## EFFECTS OF THE NEONATAL mPFC LESIONS

### Experiment 1. Spontaneous and Amphetamine-Induced Behaviors

Analysis of locomotor activity during habituation revealed that the lesioned rats did not differ from the sham operated animals in the over-all level of locomotion (a main effect of lesion $F(1,18) = 3.26$, $p = 0.09$, lesion × age interaction $F(1,18) = 0.17$, $p > .5$), but the pattern of locomotor activity was significantly different between the groups (age × time × lesion $F(11,18) = 1.78$, $p = .05$). Post-hoc analysis revealed that by the end of 1 h testing interval (at 55 min at PD35 and 25, 45, 50,

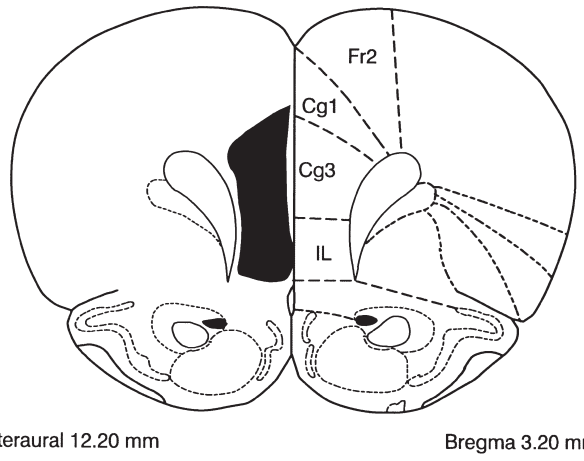


**Figure 1.** Schematic diagram of a rat brain section through the medial prefrontal cortex (from Paxinos and Watson 1986). The blackened area represents average damage produced by the excitotoxic lesion (ventral portions of area Cg1, and areas Cg3 and IL were damaged).

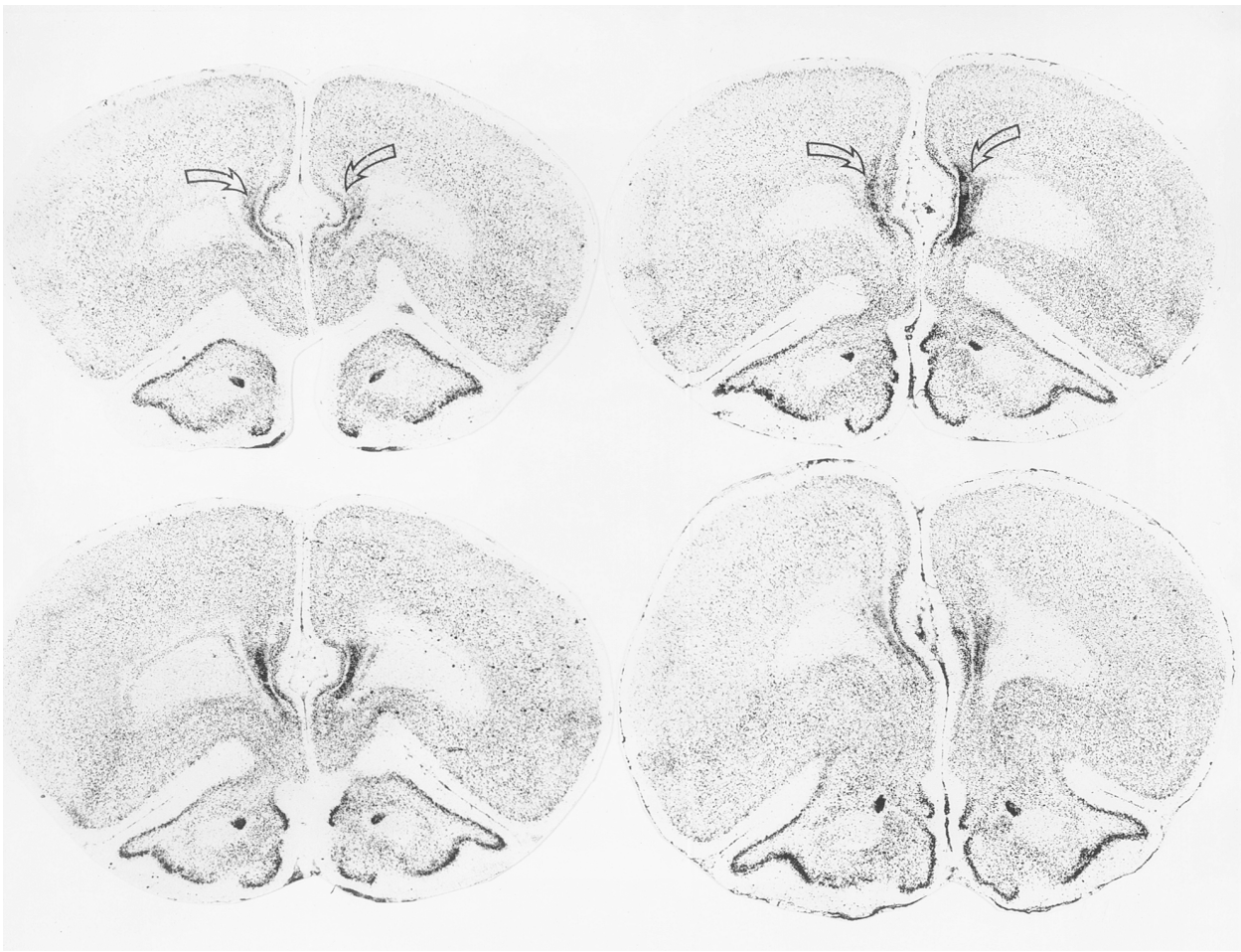

**Figure 2.** Photomicrographs of thionin-stained brain sections from rats with medial prefrontal cortical lesions induced with ibotenic acid on day 7 after birth. Arrows point to the areas of cell loss and gliosis restricted to the cingulate areas Cg1, Cg3 and parts of the infralimbic area IL of the mPFC in the anterior–posterior coordinates approximately 3.7 to 2.7 mm from bregma.

55, and 60 min at PD56, $p < .05$), locomotion after exposure to novelty was significantly attenuated in the lesioned rats (Figure 4).

After saline injection, there were no significant differences between the lesioned and control rats at any age. Amphetamine increased locomotion in both groups of animals at both ages. Although there was no difference in the over-all level of activity between the sham and lesioned rats (lesion effect $F[1,18] = 0.95$, $p > .05$), the patterns of locomotion between the groups differed significantly (age × lesion interaction $F[1,18] = 5.32$, $p = .03$), and age × lesion × time interaction $F[17,18] = 1.89$, $p = .02$). The mPFC lesioned rats showed markedly reduced locomotor activity by the end of a testing interval at PD56 (at 180–205 min, $p < .05$) but not at PD35 as compared to the controls (Figure 4B). Thus, the mPFC lesion resulted in the suppression of spontaneous locomotor activity and attenuation of amphetamine-induced locomotion at an older age.

To address the possibility that reduced locomotor activity may reflect changes in stereotypic behaviors (Whishaw et al. 1992), we compiled the number of stereotypies and stereotypy counts following amphetamine administration. An ANOVA revealed that rats with mPFC lesions displayed less pronounced stereotypies as compared to the controls (a main effect of lesion, $F[1,18] = 2.84$, $p = .1$, and $F[1,18] = 6.02$, $p = .02$, for stereotypy counts and number of stereotypies, respectively) (data not shown). Thus, attenuated locomotion observed in the mPFC lesioned rats does not seem to be caused by competing amphetamine-induced stereotypic behaviors.

### Experiment 2. Apomorphine-Induced Stereotypy

A three-way ANOVA revealed that the effect of the lesion on the level of apomorphine-induced stereotypy across the two ages was not significant (a lesion effect

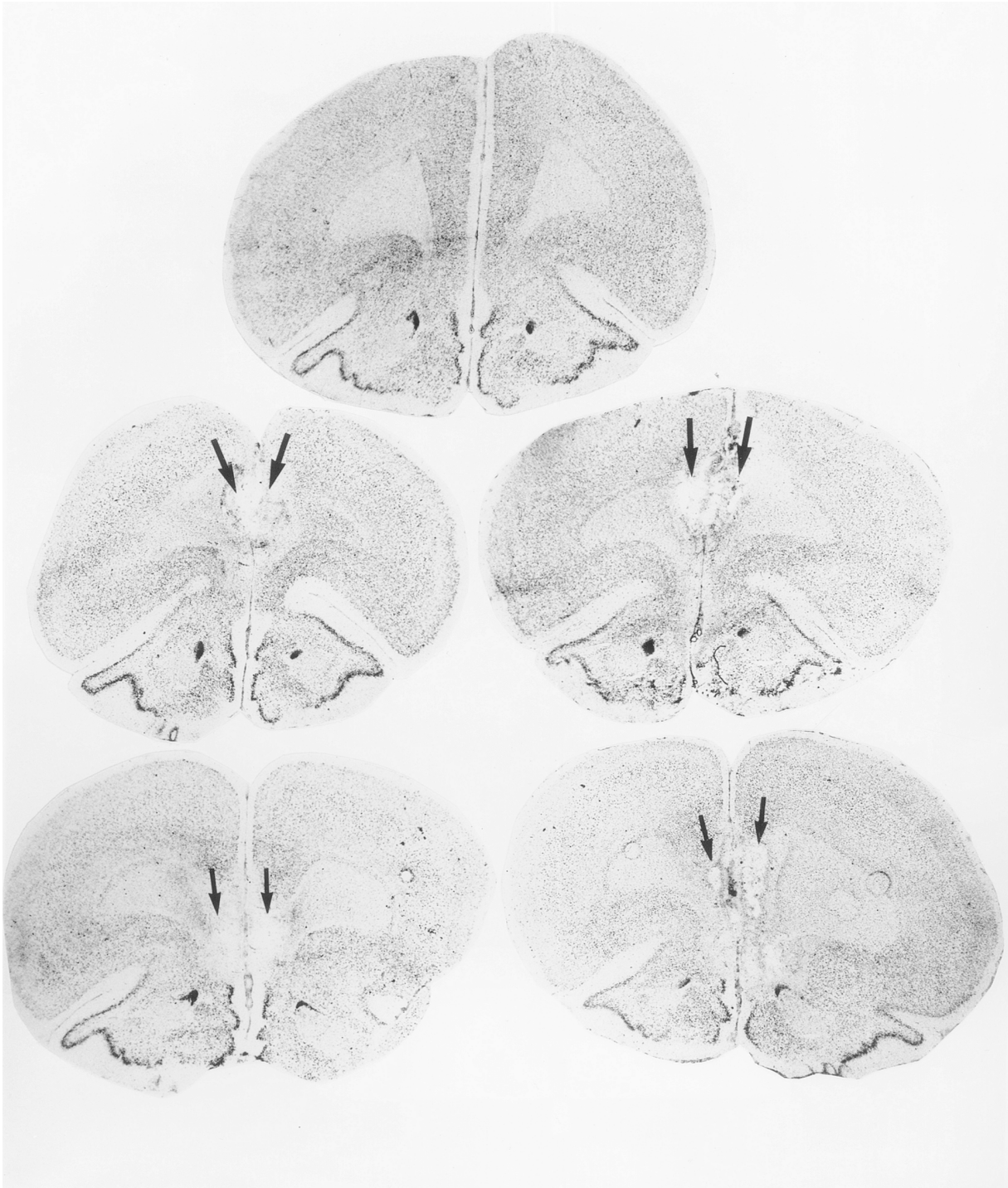

**Figure 3.** Photomicrographs of thionin-stained brain sections from rats with medial prefrontal cortical lesions induced with ibotenic acid in adulthood. Top: control sham-lesion (no damage). Bottom: ibotenic acid-induced lesions. Arrows point to cell loss, cavitation around the injection sites and gliosis.

$F[1,14] = 2.25$, $p > .1$) (Figure 5). There was, however, a difference between the groups in the age-related pattern of stereotypy (age × lesion interaction $F[1,14] = 4.45$, $p = .5$ and age × lesion × time $F[11,14] = 1.96$, $p = .03$). The activity of the control rats declined with age (by 22%, $p < .05$); whereas, the responsiveness of the lesioned rats did not significantly differ between PD35 and PD56. Thus, the lesioned rats displayed significantly more stereotypies than the control rats by PD56 (by 25%, $p < .02$) (Figure 5B). The apparent late emer-

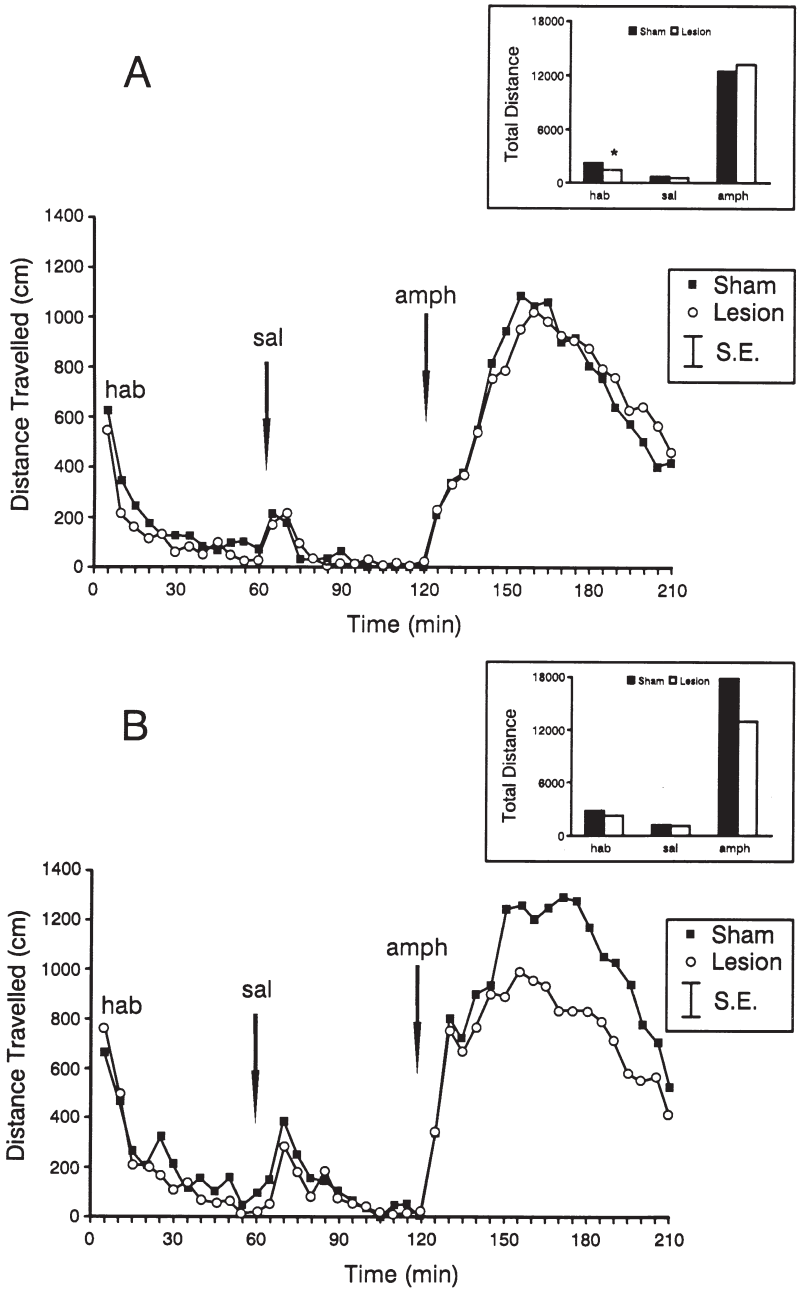


**Figure 4.** Locomotor activity of neonatally lesioned rats tested in photocell monitors at PD35 and PD56. Rats were habituated to the monitors for 60 min (hab), then injected with saline (sal, 1 ml/kg, IP) and monitored for 60 min, and finally given amphetamine (amph, 1.5 mg/kg, IP), and monitored for an additional 90 min. The same rats were tested at PD35 **(A)** and PD56 **(B)**. Inserts show total distance traveled during each testing interval. The lesioned rats displayed less locomotor activity when exposed to a novel testing environment at PD35 and tended to be hypoactive after amphetamine at PD56 (SE = standard error of mean).

gence of increased sensitivity to apomorphine in the lesioned rats may thus be attributable to the absence of declining levels that were seen in controls.

### Experiment 3. MK-801-Induced Hyperlocomotion

During a 30 min habituation period, the lesioned rats displayed significantly attenuated locomotion as compared to the sham-operated animals (by 18%, total distance for the sham and lesion groups 2844 cm ± 169 and 2321 cm ± 187, respectively). A two-way ANOVA showed a significant main effect of lesion ($F[1,41] = 4.28$, $p < .05$) and time ($F[5,41] = 274.0$, $p < .001$), but no significant lesion × time interaction ($F[5,41] = 1.38$, $p > .1$) (Figure 6).

A three-way ANOVA of the locomotor response to MK-801 demonstrated that all three doses of MK-801 increased locomotion in the sham and lesioned animals as compared to a saline injection (a main effect of drug $F[3,41] = 22.0$, $p < .0001$). The over-all activity of the lesioned rats differed significantly from the controls (a main effect of lesion $F[1,41] = 4.1$, $p = .05$), but the changes were not time- or dose-related (no significant lesion × drug interaction $F[3,41] = 1.5$, $p > .2$ or lesion × drug × time interaction $F[11,41] = 0.81$, $p > .5$) (Figure

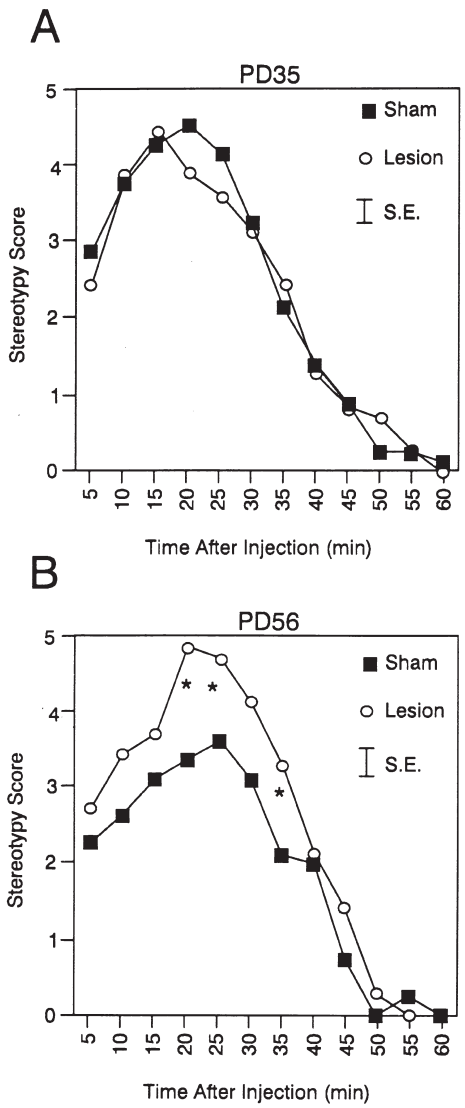


**Figure 5.** Stereotypy scores after administration of apomorphine (0.75 mg/kg SC) in rats with neonatal lesions of the medial prefrontal cortex tested at PD35 **(A)** and PD56 **(B)**. The lesioned rats showed significantly more stereotypic behaviors than control rats at PD56 (SE = standard error of mean).

7A–D). Post-hoc analysis revealed that the lesioned rats were less active after saline and after 0.2 mg/kg of MK-801 ($p < .05$) as compared with sham controls.

## IN SITU mRNA HYBRIDIZATION HISTOCHEMISTRY

Although the levels of $D_1$ and $D_2$ mRNA were somewhat higher in the PFC-lesioned rats than in the sham-operated controls, the differences did not reach statistical significance for any of the striatal regions analyzed (Table 1).

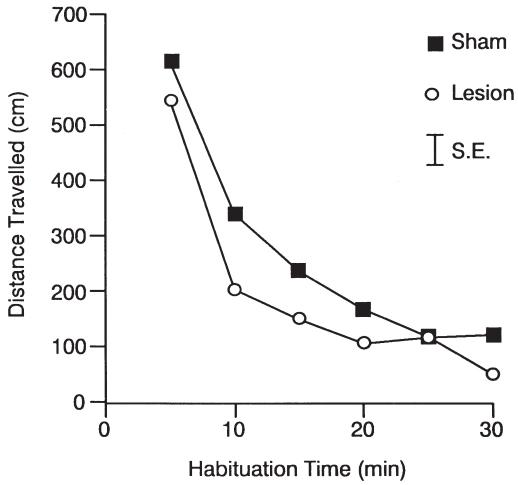


**Figure 6.** Locomotor activity in response to a novel environment (rats were placed in photocell monitors). During a 30 min habituation period, the lesioned rats displayed significantly attenuated locomotion as compared to the sham-operated animals (SE = standard error of mean).

## ADULT LESION OF THE mPFC IN RATS WITH NEONATAL HIPPOCAMPAL DAMAGE

A two-way ANOVA showed a significant effect of the VH lesion on locomotion during a habituation period ($F[1,37] = 6.4$, $p < .05$), but no significant effect of the mPFC lesion ($F[1,37] = 0.3$, $p > .5$) or interaction between VH and mPFC lesions ($F[1,37] = 1.4$, $p > .1$). The results of a post-hoc test revealed that the rats that had received a neonatal lesion of the ventral hippocampus followed by a sham lesion of the mPFC displayed significantly more locomotion than either sham VH/sham mPFC or sham VH/lesion mPFC groups ($p = .01$ and $p = .04$, respectively), Figure 8A. The effects of VH and mPFC lesions on locomotion after saline injection ($F[1,37] = 0.03$, $p > .5$; $F[1,37] = 0.3$, $p > .5$, respectively) or the interaction between the two ($F[1,37] = 0.04$, $p > .5$) were not significant (data not shown). There were significant effects of both lesions (mPFC $F[1,37] = 7.5$, $p < .01$, VH $F[1,37] = 7.1$, $p = .01$) on locomotor activity after amphetamine, but the interaction was not significant ($F[1,37] = 3.6$, $p = .06$). Post-hoc testing revealed that rats with the neonatal hippocampal lesion followed by the sham mPFC lesion were hyperactive as compared to both sham hippocampal controls (with subsequently sham-operated or lesioned mPFC, $p = .002$ and $p = .0002$, respectively) as well as compared to the rats with the neonatal hippocampal lesion followed by the adult mPFC lesion ($p = .005$), Figure 8B. The mPFC lesion did not, by itself, alter locomotor response to amphetamine (sham VH/lesion mPFC not different from sham VH/sham mPFC, $p > .5$). The mPFC lesion, however, suppressed hyperlocomotion induced by the neonatal hip-

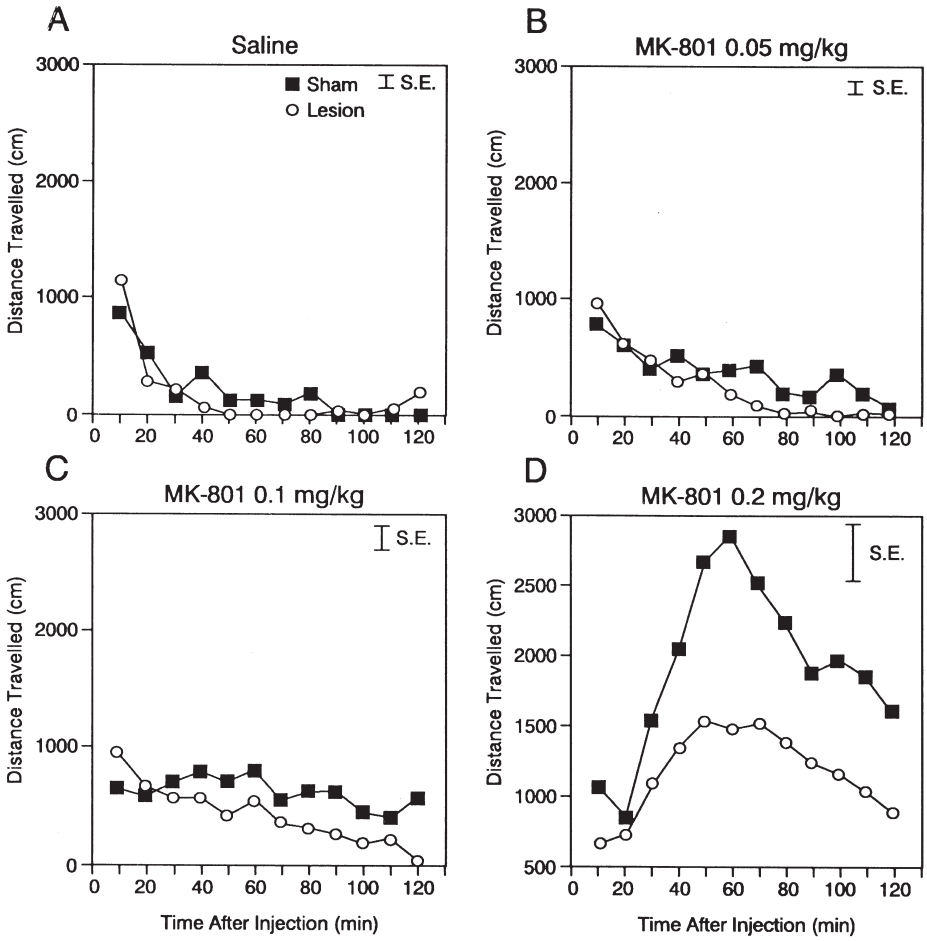


**Figure 7.** Locomotor activity of rats with neonatal lesions of the medial prefrontal cortex in response to MK-801. At PD56, rats were randomly assigned to receive either saline **(A)** or one of three doses of MK-801 **(B-D)** (0.05, 0.1 or 0.2 mg/kg, SC), and were monitored for 120 min. The lesioned rats tended to display less locomotion in response to MK-801 than controls (SE = standard error of mean).

pocampal damage, because rats with both brain regions lesioned (VH and mPFC) no longer displayed enhanced amphetamine-induced behavior.

## DISCUSSION

The results of our study demonstrate that neonatal excitotoxic lesions of the mPFC did not result in exacerbated novelty-, amphetamine- or MK-801-induced locomotor activity either pre- or postpuberty. To the contrary, these behaviors were attenuated in the lesioned animals. This contrasts dramatically with the effects of neonatal excitotoxic lesions of the VH. The mPFC lesions did result, however, in augmented apomorphine-induced stereotypic behaviors at a postpubertal age. Although previous findings linked stereotypy to increased stimulation of dopamine receptors (Waddington et al. 1990), the mPFC lesion did not elevate expression of striatal $D_1$ or $D_2$ receptor mRNA.

These data suggest that certain aspects of dopaminergic neurotransmission; that is, those reflecting postsynaptic function (apomorphine-induced stereotypic behaviors), resembled effects observed after a similar mPFC lesion induced in adult animals (Braun et al. 1993; Lipska et al. 1995b; Jaskiw et al. 1991); whereas others; that is, the behavioral measures of presynaptic dopaminergic function (novelty- and amphetamine-induced locomotion), were different than in the adult mPFC lesioned rats (increased or unchanged in Jaskiw et al. 1990, Braun et al.; Schaub et al. 1997, attenuated in the current study). The reasons for these differences may be two-fold. First, the neonatal lesion in this study may be more confined to the ventral portions of the mPFC (infralimbic/prelimbic IL/PL[Cg3] regions) as compared to the more widespread lesion in the previous studies in adults, which comprised the PL (Cg3), the entire anterior cingulate area (Cg1 and ACd), and portions of the precentral medial area (FR2 or PrCm) (Jaskiw et al. 1990. Lipska et al. 1995b). The two latter regions are considered to be part of the sensorimotor cortex and are primarily involved in motor functions (Zilles and Wree 1995). They have different afferent inputs (from the somatosensory cortex, Berendse et al. 1992), a different pattern of projections to the striatum (to more caudal and lateral striatal areas as compared with more rostral and medial projections to the striatum arising from the PL (Cg3) and IL (Conde et al. 1995), and to the nucleus

**Table 1.** Striatal Expression of $D_1$ and $D_2$ mRNA Assessed by in Situ Hybridization Histochemistry in Rats with Neonatal Excitotoxic mPFC Damage

| | mRNA, $D_1$ | | mRNA, $D_2$ | |
|---|---|---|---|---|
| **Brain Region** | **Sham** | **Lesion** | **Sham** | **Lesion** |
| Whole striatum | 4.766 ± 0.168 | 5.112 ± 0.144 | 6.072 ± 0.168 | 6.384 ± 0.144 |
| Dorsolateral striatum | 4.752 ± 0.168 | 5.112 ± 0.168 | 6.288 ± 0.192 | 6.528 ± 0.168 |
| Dorsomedial striatum | 4.656 ± 0.144 | 4.992 ± 0.144 | 6.336 ± 0.240 | 6.504 ± 0.168 |
| Ventral striatum | 5.088 ± 0.168 | 5.496 ± 0.240 | 6.072 ± 0.216 | 6.384 ± 0.192 |
| N. accumbens core | 4.704 ± 0.168 | 5.208 ± 0.168 | 5.928 ± 0.168 | 6.480 ± 0.264 |
| N. accumbens shell | 5.928 ± 0.216 | 6.168 ± 0.014 | 6.024 ± 0.144 | 6.072 ± 0.264 |

Striatal regions are subdivided according to the Paxinos and Watson atlas (1986). In situ hybridization data are expressed as dpm/mm$^2$, and represent the mean ± SEM of pooled values obtained from four sections per animal (lesion, $n = 7$, sham, $n = 8$). ANOVA did not show significant differences between the lesioned and sham-operated animals.

accumbens (dorsal PL (Cg3), ACd (Cg1), and PrCm (F2) projecting to the core, IL to the shell of the n. accumbens (Brog et al. 1993), as well as different functions (Seamans et al. 1995, Deutch et al. 1993) than the IL/PL (Cg3) regions. Second, a neonatal lesion may allow more sparing or recovery of function than a similar adult lesion. Although there are many variables to be considered when comparing the effects of brain damage between different studies, age at lesion is one with the greatest impact on the behavioral outcome (Kennard 1936; Goldman 1971; Goldman 1974; Kolb 1990; Kolb et al. 1987; Kolb and Gibb 1990; Kolb and Sutherland 1992; Wood et al. 1997). Very early cortical lesions (first 5 days of life) are reported to cause pronounced abnormalities; whereas, cortical damage around 10 days of age yields maximal sparing (Kolb 1990; Kolb and Sutherland). Other important variables include the lesion size (i.e., smaller cortical lesions allow more sparing; in this study, relatively small damage may explain few deficits), and the specificity of the task (in this study, animals seemed to be only mildly impaired in novelty-, amphetamine- or MK-801-induced locomotion, but may display more severe deficits in more complex behaviors). Thus, taking into account these multiple factors that may influence behavioral outcome, it is not surprising that the relatively restricted lesion of the mPFC in neonates resulted in milder and somewhat different behavioral abnormalities than previously reported damage inflicted in adulthood.

Surprisingly, the results of our study do not agree with the findings of Flores et al. (1996b), who report that neonatal (day 7 after birth) excitotoxic lesions of the mPFC result in postpubertal emergence of novelty- and amphetamine-induced hyperlocomotion and markedly increased expression of striatal $D_2$ receptors as indicated by increased $D_2$ mRNA expression in all striatal/accumbens subregions and increased [3-H]-YM-09151-2 binding in the shell of the nucleus accumbens. One possible explanation of these discrepancies is that our lesion encompasses a more ventral portion of the mPFC than that described by Flores et al. (1996b). This possibility is likely, because although the lesion boundaries in the schematic drawing in their study (Figure 1 in Flores et al. 1996b) are similar to the boundaries of our lesion, their photomicrograph of the lesion (Figure 2) suggests that only more dorsal aspects of the mPFC have actually been damaged (i.e., area F2 or PrCm). It should be pointed out, moreover, that these dorsal prefrontal cortical regions do not receive direct projections from the hippocampus, as do the PL and IL (Swanson 1981; Jay et al. 1989; Jay and Witter 1991; Ferino et al. 1987; Laroche et al. 1990). There is also no indication that the more dorsal mPFC would contribute more to the regulation of subcortical dopamine function than the ventral parts. To the contrary, for example, the PL/IL regions, but not the shoulder cortices, have been implicated in neurochemical responses to stress (Deutch et al. 1993).

The results of our study further demonstrate that if the neonatal mPFC lesion involves predominantly areas innervated by the VH, then the behavioral consequences of such lesions are in striking contrast to the effects of neonatal excitotoxic lesions of the VH itself. These latter lesions were consistently reported to result in postpubertal emergence of markedly enhanced locomotor responsiveness to stress, amphetamine, and MK-801 (Lipska et al. 1993; Wan et al. 1996; Wan and Corbett 1997; Flores et al. 1996a; Black et al. 1996; Al-Amin et al. 1997). So far, the mechanisms of these behavioral alterations have not been identified. Although the behavioral changes suggest increased dopaminergic function, enhanced dopamine release or dopamine receptor abundance have not been detected in subcortical regions (Knable et al. 1994; Wan et al. 1996; Lipska et al. 1995c; Lillrank et al. in press).

Some of the earlier data pointed to possible involvement of the mPFC in the hippocampal lesion-induced behavioral disruptions (Chambers et al. 1996; Lillrank

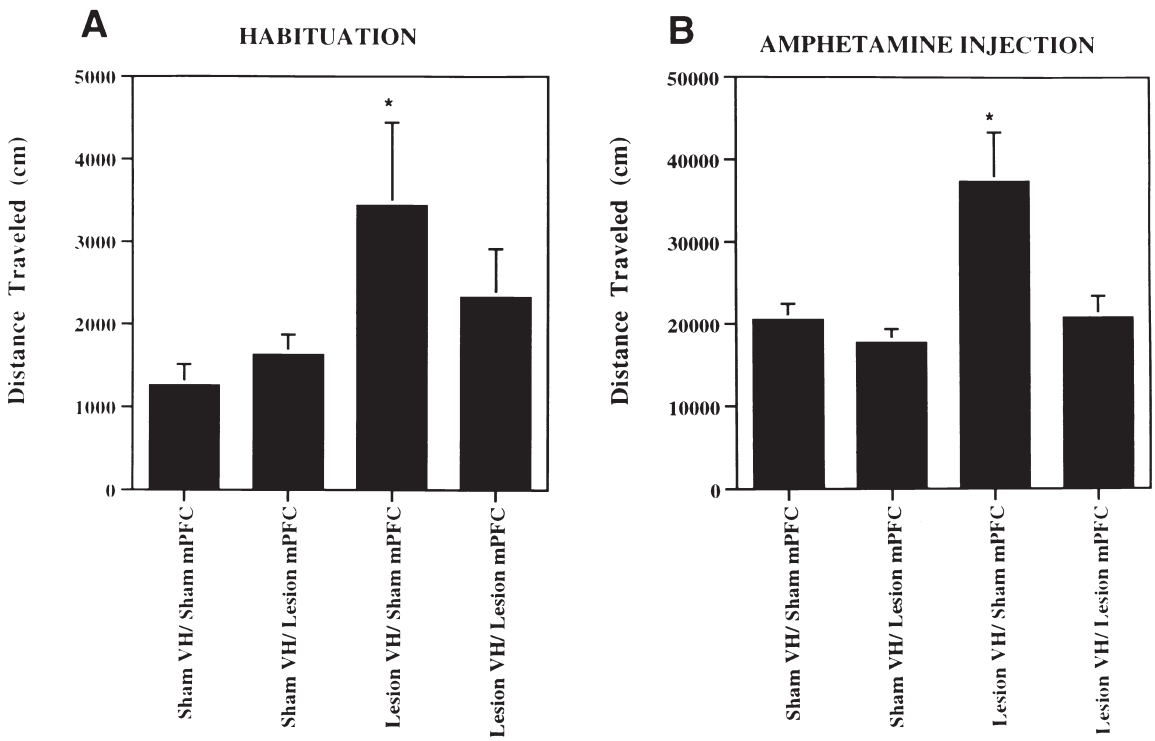


**Figure 8.** Locomotor activity of rats with lesions of the ventral hippocampus (VH) produced in early postnatal life (PD7), and with subsequent lesions of the medial prefrontal cortex (mPFC) produced in adulthood. Rats were tested in photocell monitors 4 weeks after the second lesion. They were habituated to the monitors for 60 min **(A)**, then injected with saline (1 ml/kg, IP), monitored for 60 min, and given amphetamine (1.5 mg/kg, IP), and monitored for an additional 90 minutes **(B)**.

et al. 1996; Al-Amin et al. 1997, Sams-Dodd et al. 1997). We speculated that neonatal deafferentation of the mPFC by the excitotoxic hippocampal lesion might alter the response of mPFC neurons to various stimuli and result in anomalous regulation of projections to subcortical sites, thus contributing to aberrant hyperdopaminergic behaviors. The present data are consistent with such a possibility. Removal of the presumably dysfunctional mPFC in the animals with previous developmental damage of the hippocampus, normalized their behaviors in the amphetamine test. It is noteworthy that recent findings in the primate also suggest that early postnatal damage of the hippocampus alters in adulthood the mechanisms whereby PFC regulates subcortical dopamine function as revealed by in vivo microdialysis in response to intra-PFC amphetamine infusion (Saunders et al. 1998).

Understanding the neurobiological basis for the abnormal behaviors associated with the neonatal hippocampal and prefrontal cortical lesions may provide insight into the pathophysiological mechanisms involved in schizophrenia. In schizophrenia, subtle maldevelopment of prefrontal–temporal-limbic cortices and abnormal dopamine and glutamate function have been reported. Psychotic symptoms in schizophrenics appear after puberty and are exacerbated by dopamimetics (e.g., amphetamine), NMDA antagonists (e.g., ketamine or MK-801), and stressful events. Our findings demonstrate that neonatal excitotoxic damage of the ventral hippocampus, but not of the prefrontal cortex, provides a heuristic model of these aspects of schizophrenia, including prefrontal cortical malfunction. Moreover, these data suggest that at least some of the abnormal phenomena observed in the animals with the neonatal VH damage depend upon the presence of intrinsic PFC neurons that developed in the context of abnormal temporal-limbic connections.

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