Both Electrolytic and Excitotoxic Lesions of Nucleus Accumbens Disrupt Latent Inhibition of Learning in Rats


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Evidence indicating a role for the nucleus accumbens in the development of latent inhibition of learning has accumulated. Two experiments were conducted using Wistar rats to investigate this role directly. Experiment 1 used a conditioned emotional response paradigm to assess the effects of discrete electrolytic lesions in the shell region of the nucleus accumbens. Latent inhibition was attenuated by this lesion. In order to determine the contribution made by damage to fibers en passage associated with electrolytic lesions, Experiment 2 assessed the effects of NMDA-induced lesions in the shell of the nucleus accumbens in the same task. Latent inhibition was again significantly attenuated. These findings support the proposition that an intact nucleus accumbens is necessary for the normal development of latent inhibition.

INTRODUCTION

When animals are preexposed to a stimulus without consequence, they are subsequently slower to associate this stimulus with an important event, such as footshock. This retarding effect of stimulus preexposure is called latent inhibition (LI) (Lubow & Moore, 1959) and can be demonstrated in a variety of classical and instrumental paradigms and in a wide range of species, including human (see Lubow, 1989, for review). The development of LI has been considered to reflect learning to ignore irrelevant stimuli (Lubow, 1989; Mackintosh, 1973, 1975; Schmajuk & Moore, 1985). Alternative ac-

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3 The authors thank Sara Fearn for the preparation of histology. This research was supported by an Overseas Research Award (UK) to Chih-Ta Tai and by Bristol-Myers-Squibb. Address correspondence and reprint requests to Dr. J. N. P. Rawlins, Department of Experimental Psychology, South Parks Road, Oxford OX1 3UD, England. Fax: +44 865 310447.
1988), considered to act primarily via the N. Acc. Such doses enhance locomotor activity; this effect has been attributed to a selective drug action on ventral striatum (Creese & Iversen, 1975; Solomon & Staton, 1984). Under the same experimental conditions, LI is not affected by high doses of amphetamine (Weiner, Izraeli-Telerant, & Feldon, 1987). Dopamine overactivity within the N. Acc. has been given a central role in the disruption of LI in two recent models of the neural substrates of LI (Gray et al., 1991; Weiner, 1990). Recent anatomical evidence shows that a pathway from ventral subiculum to N. Acc. runs down the lateral edge of the septum and that this pathway terminates primarily in the medial portion of N. Acc. (Groenewegen, Vermeulen-Van der Zee, TE Kortschot, & Witter, 1987) on the same neurons in the N. Acc. that receive dopaminergic input from the ventral tegmentum (Nauta, Smith, Faull, & Domesick, 1978; Swanson & Cowan, 1975; Totterdell & Smith, 1989). It has been suggested that disruption of these connections plays an important role in the development of schizophrenia (Gray et al., 1991). Moreover, a recent postmortem study has revealed a marked loss of neurons in the N. Acc. itself in the brains of chronic schizophrenic patients (Pakkenberg, 1990). Experiment 1 therefore assessed the effects of discrete electrolytic lesions in N. Acc. on the development of LI. Experiment 2 used the same paradigm to assess the effects of cytotoxic lesions in N. Acc., to determine whether the effects of the lesions that we observed in Experiment 1 could best be attributed to lesion-induced loss of cell bodies or to damage to fibers en passage through the area of the lesion.

MATERIALS AND METHODS

Animals

Each experiment used 48 male albino Wistar rats (Charles River Ltd.) as subjects. They were approximately 5 months old and were housed 1 to a cage in a temperature- and humidity-controlled room with lights on from 8:00 AM to 8:00 PM. Upon delivery, subjects were maintained on ad lib food and water for 14 days prior to the commencement of surgery. Following surgery, the animals were returned to their home cages and allowed 12–15 days of recovery. Prior to their participation in the present experiments, the animals in both of the present experiments had been trained to run in an alley (under conditions of partial or continuous reinforcement) for food reward and then extinguished; reported elsewhere for the electrolytic lesion (Tai, Clark, Feldon, & Rawlins, 1991). During this time, the animals were maintained on a 23-h food deprivation schedule, with water freely available. They were returned to an ad lib schedule of food and water for 2 weeks before being allocated to experimental groups for the present experiments (for which they were counterbalanced with respect to the reinforcement schedule they had experienced in the previous runway experiments).

Surgery

Experiment 1. The rats were anesthetized by intraperitoneal injection of Avertin at a dose of 10 ml/kg (Avertin concentrate consists of 100 g of 2,2,2-tri-bromo-ethanol dissolved in 62 ml of tertiary amyl alcohol: 1.25 ml of this concentrate are added to 5 ml absolute alcohol and 62.5 ml of 0.9% saline). They were placed in the ear-bars of a David Kopf stereotaxic frame; an incision was made into the scalp and the skull was exposed. A small square of bone was removed from the skull starting approximately at bregma and extending rostrally about 4 mm. The dura thus exposed was carefully incised and parted. Bilateral electrolytic lesions were made in 24 subjects (Electro group) by passing a 1-mA, 9-s current bilaterally via a 30-gauge stainless-steel electrode (anodal), insulated except for 0.5 mm at the tip. A constant-current DC source was used. The stereotaxic level-head coordinates were AP 1.5 mm anterior to bregma, ±1.0 mm lateral from the midline, 6.4 mm deep from brain surface (Paxinos & Watson, 1986). A clip on the rat’s ear served as cathode. In control animals (Sham group, n = 24), the surgical procedure was as described above but no insertion of electrode was made. The coordinates and lesion parameters were derived from pilot studies. After surgery, the scalp incision was sutured with Michel clips, sulfonamide powder was sprinkled on the wound, and the rat was returned to the home cage. One animal in the Sham group died following surgery.

Experiment 2. All animals were anesthetized and prepared as described above for Experiment 1. A 30-gauge needle fitted to a Hamilton microsyringe was used to make two injections of 0.5 μl 0.08 M NMDA (prepared in phosphate buffer) on each side of the brain in 24 animals (NMDA group), while vehicle (VEH) injections were made in another 12 animals (VEH group). A further 12 animals had the skull exposed and the same area of bone removed, but no needle lowered (Sham group). The stereotaxic level-head coordinates were AP +1.0 and +1.7 mm
anterior to bregma, ± 1.0 mm lateral from the midline, 6.4 mm deep from brain surface.

Apparatus

The apparatus consisted of eight modified Campden Instruments CI 460 rat operant chambers, each located in a ventilated sound-insulated Campden Instruments chest. The lever holes had been sealed by stainless steel plates and the food tray had been modified to allow the presentation of the spout of a water bottle into the chamber. The tip of the spout was recessed 4 mm behind an annular metal plate. This had been designed such as to prevent the rat touching the tip of the water spout with anything other than its tongue. Licks were detected by a Campden Instruments drinkermeter (Model 453) and simultaneously recorded on a Data General Nova 4 C and the data transferred to a Tandon PC. The preexposure phase consisted of a total of 50 (25 on each of 2 consecutive days) 5-s presentations of a flashing 2.8-W house light: the bulb was on for 300 ms and off for 300 ms throughout the presentation period. Footshock was delivered through a grid floor by Campden Instruments Model 521 shock sources and scramblers.

Behavioral Procedures

The subjects were placed on a 23-h water deprivation schedule 5 days before baseline training commenced. Water was presented at the same time every day. Each animal was allocated to one of two Exposure conditions (preexposed, PE, or nonpreexposed, NPE). The rats were tested in squads of eight at a time; each squad consisted entirely of NPE rats or PE rats, but as far as possible with an equal number of rats from each lesion condition.

Baselining

The rats were individually placed into the chambers with the house lights on throughout the session and allowed to make licks freely for 30 min each day for 5 days. All eight boxes were used simultaneously. Each animal was always tested in the same box and then returned to the home cage. Forty minutes of further access to water was given there, at the usual time each day.

Preexposure

On Days 6 and 7, each animal was placed in its appropriate box, with the house light on, but with the drinking bottle removed. On each of these days, the PE animals received 25 presentations of flashing light, distributed according to a random interval schedule with a mean value of 64 s. The NPE animals were confined to the box for an identical period of time with the house light on continuously as usual.

Conditioning

On Day 8, subjects were placed in the allocated boxes, with the house light on, but with the drinking bottles removed. Each animal was given two flashing-light–shock pairings. The shock delivered was 0.65 mA × 1 s and was given immediately following the 15-s presentation of the flashing light. The first light–shock pairing was given 5 min after the start of the conditioning session; the second was 5 min later. After the second pairing, the animals were left in the experimental chambers for an additional 5 min.

Rebaselining

On the following day, the animals were given 1 day of rebaselining using the procedure described above for baselining.

Test

On the next day, each animal was placed in the appropriate chamber and tested using the same procedure as in baselining except that the house light started to flash 120 s after the beginning of the session and continued to do so for 15 min. The following measures were recorded: drinking performance before the light CS was presented, measured as the time taken to make the 25 licks preceding CS presentation (Pre-CS period); drinking performance throughout CS presentation, measured as number of licks in each of 15 successive 1-min “Bins”; and drinking behavior over the entire test session, measured as the total number of licks. The time units employed were 1/50 s. In this design, LI is demonstrated to the extent that PE animals learn less about the light–shock association. Reduced learning results in less conditioned suppression of drinking, and this is reflected in an increased licking in the presence of the flashing light. The analysis of licks per minute following the presentation of the stimulus allows a temporal separation of the point at which the rat begins to lick freely and satiation. Thus, although total licks over 15 min might be numerically similar for PE and NPE groups, the pattern of drinking over time may yield
Important information about the animals' response to the stimulus.

Statistical Analysis

Analyses of variance (ANOVAs) were conducted using the statistical package BMDP on a digital equipment corporation VAX running the VMS operating system. Total numbers of licks and pre-CS periods were independently analyzed using two-way ANOVAs with main effects of Exposure and Lesion. Licks during each 1-min Bin following the beginning of stimulus presentation were analyzed using ANOVA with repeated measures. Post hoc comparisons were made by t test based on the pooled error term derived from the appropriate stratum of the ANOVA, with p < .05 as the accepted level of significance. In Experiment 2, further contrasts were conducted using BMDP 4V, with significance levels adjusted for multiple comparisons.

Histology

At the end of the behavioral experiments, the animals were overdosed with sodium pentobarbital and perfused transcardially with isotonic saline followed by 10% formalin. The brains were removed and sectioned at 50 μm on a sledge microtome. Every third section was saved and stained with cresyl violet. The histological examination was carried out without knowledge of the behavioral results.

RESULTS

Histology

Experiment 1. A representative section of the Electro groups is presented in Fig. 1. The maximum
and minimum extent of the lesions are shown in Fig. 2. Four animals were excluded from the Electro groups on the basis that they had insufficient damage in N. Acc. All of the animals retained had bilateral damage in N. Acc. The accumbens damage was typically restricted to the rostral and medial portions and never included the caudo-lateral portions. There was minimal damage to the caudate-putamen. There was no bilateral dorsolateral septal damage, but seven animals had some ventrolateral septal damage. This was unilateral in five animals, and bilateral but restricted in two. None of these animals was excluded. (The histological results in Exp. 1 have been presented elsewhere (Tai et al., 1991), but are duplicated here for the reader's convenience.)

Experiment 2. A microphotograph taken from a representative subject and a reconstruction of the lesion are presented in Figs. 3 and 4. Six animals from the NMDA groups were excluded: three rats were excluded on the basis that they did not have sufficient damage in N. Acc. bilaterally, while another three were excluded because there was significant damage in the overlying septum. All of the animals retained had bilateral damage in N. Acc. The accumbens damage was typically restricted to the medial portions and did not include the lateral portions. There were no obvious signs of tissue collapse in N. Acc. However, since this possibility cannot be altogether eliminated when assessing only Nissl-stained material, the area of neuronal depletion may have been greater than it appeared. There was minimal damage to the caudate-putamen.

Behavior

Experiment 1. One further animal was excluded because it failed to make 25 licks before the flashing light started, leaving group sizes as follows: Sham-PE, 10; Sham-NPE, 12; Electro-PE, 10; Electro-NPE, 10.

The lesion did not affect drinking behavior as such (Table 1). Both lick rates during the pre-CS period (time taken to finish the last 25 licks prior to the presentation of the flashing-light CS) and the total number of licks during the whole test session did not differ significantly between the four groups (Sham/Electro-PE/NPE); the analysis showed neither significant differences between lesion or exposure conditions nor any significant interactions (results of statistical analyses shown in Table 1).

There was clear LI in the control subjects: the rats that had not been preexposed to the light-CS showed marked suppression of licking when the CS was presented; the rats that had been preexposed showed less conditioning to the CS, as indexed by their comparatively rapid lick rate following CS onset (see Fig. 5). On the other hand, the rats in the Electro group showed no clear LI. The Electro-NPE group tended to lick more than the Sham-NPE group, and the Electro-PE group tended to lick less than the Sham-PE group. The ANOVA showed no significant main effects, but there were significant 2- and 3-way interactions with Bins (Bins × Exposure and Bins × Exposure × Lesion [F(14, 532) = 2.67, p < .001; 2.41, p < .01, respectively]. There was also a significant 3-way interaction between Exposure, Lesion, and the linear component of Bins [F(1, 38) = 8.53, p < .01]. The post hoc tests showed that there was significant LI in the controls in Bins 1–3 (see Fig. 5). The two Electro groups (PE and NPE) lay midway between the two Sham control groups (PE and NPE) during
NUCLEUS ACCUMBENS AND LATENT INHIBITION

FIG. 3. (A) Photomicrograph (×20) of a cresyl violet-stained coronal section of rat brain showing bilateral NMDA lesions aimed at the shell region of nucleus accumbens; the centers of the injections are visible as patches of dense gliosis close to the islet of Calleja. The bar at lower left indicates 1 mm. (B) Enlargement (×100) of the rectangular region outlined in A. Extensive granulocytosis and loss of neurons can be seen in the shell area of nucleus accumbens below the tip of the lateral ventricle and medial to the anterior commissure (which can be seen toward the lower left-hand corner). Intact neurons can be seen in the area outside the lateral ventricle and, at the bottom of the enlargement, below the anterior commissure. Some intact medial septal and diagonal band cells can be seen to the right of the enlargement. The bar at upper left indicates 0.5 mm.

this period of testing. The only significant differences between the two Electro groups (PE and NPE) emerged later in testing, when a reversed LI effect was seen, significant in Bin 6 and marginal (p = .05) in Bin 7.

Experiment 2. One animal in the VEH–PE group was excluded because it failed to make 25 licks before the flashing light started, leaving group sizes as follows: Sham–PE, 6; Sham–NPE, 6; VEH–PE, 5; VEH–NPE, 6; NMDA–PE, 10; NMDA–NPE, 8.

The cytotoxic lesions did not affect overall drinking behavior as such. The pre-CS periods (time taken to finish the 25 licks prior to the presentation of the flashing light) were more variable than those seen in Experiment 1, but nonetheless the six experimental groups (described above) did not differ significantly. The analysis showed neither significant differences between Lesion or Exposure conditions nor any significant interactions (Table 1).

As in Experiment 1, there was clear LI in Sham control subjects: the rats that had not been preexposed to the light–CS showed marked suppression of licking when the CS was presented; the rats that had been preexposed showed less conditioning to the CS, as indexed by their comparatively rapid lick rate following CS onset (see Fig. 6). LI was, if anything, clearer still in the vehicle control group (com-
pare VEH–PE and VEH–NPE). There was no evidence of LI in the NMDA lesion group (compare NMDA–PE and NMDA–NPE), because the NMDA–PE subjects showed suppression of drinking that was equivalent to that shown by the rats in all three NPE groups.

The ANOVA showed no significant main effect of Lesion, but there was a significant main effect of Exposure \(F(1, 35) = 11.68, p < .01\) and there were significant 2- and 3-way interactions: Bins \(\times\) Exposure \(F(14, 490) = 4.36, p < .001\), Bins \(\times\) Lesion \(F(28, 490) = 2.03, p < .05\), and Bins \(\times\) Exposure \(\times\) Lesion \(F(28, 490) = 2.49, p < .01\). There was also a significant 3-way interaction between Exposure, Lesion, and the linear component of Bins \(F(2, 35) = 5.33, p < .01\).

Inspection of Fig. 6 reveals that there was graphically clear LI in the Shams over the first 5 min of test, which was statistically significant in Bins 2 and 4 and that there was significant LI in the VEH group over the first 6 min of test, but that there was no significant LI in the NMDA group. These marked effects were confirmed by the post hoc contrasts, which demonstrated that there were significant differences between PE and NPE animals (that is, LI was present) in both Sham and VEH groups \(F(14, 490) = 1.78, p < .05; 5.22, p < .001\) respectively), but not in the NMDA group \(F(14, 490) = 1.15, \text{n.s.}\). The NMDA–PE group clearly differed from the Sham–PE \(F(14, 490) = 2.91, p < .001\) and VEH–PE groups \(F(14, 490) = 6.87, p < .001\). There were no significant differences among the three NPE groups, although there were slight differences between the lesion conditions in lick rates over the first 5 min of the test (Sham, 25.0 licks/min; VEH, 0.33 licks/min; NMDA, 31.2 licks/min).

The lesion produced no significant change in overall drinking: an analysis of total licks (combining pre-CS and drinking throughout CS presentation)
FIG. 4. Line drawings illustrating reconstructions of the largest (stippled) and smallest (black) lesions retained in Exp. 2 (NMDA lesion).

yielded only a main effect of Exposure \( F(1, 35) = 10.72, p < .01 \), reflecting the strong LI in the VEH and Sham conditions discussed above. There was no effect of Lesion or interaction involving Lesion (results of statistical analyses shown in Table 1).

**DISCUSSION**

Sham-operated control rats showed statistically clear LI in both experiments. Rats with small lesions in the shell area of nucleus accumbens showed significantly attenuated LI. This was clear both when conventional electrolytic lesions were assessed in Experiment 1 and when cell body lesions, made using an axon-sparing excitotoxin, were assessed in Experiment 2. Vehicle control rats in Experiment 2 also showed LI that was, if anything, enhanced by the injection procedure, with respect to Sham-operated controls. These effects cannot be attributed to any overt changes in overall drinking behavior since there were no significant effects of either lesion on measures of pre-CS licking or total licking overall (see Table 1). Moreover, there was no tendency for drinking in the first few minutes of CS presentation to depend on lick rate in the pre-CS period: in Experiment 2, the three groups drinking fastest prior to CS delivery included both the group that drank slowest (VEH–NPE) and the group that drank fastest (VEH–PE) in the presence of the CS (see Table 1).

Although the lesions effectively prevented the development of normal LI, it is nonetheless important to identify the way in which they exerted their effects. The electrolytic N. Acc. lesion (Experiment 1) attenuated LI in part because licking in the Electro–NPE group was less suppressed than that in the Sham–NPE rats. Had there been no disinhibition in the Electro–NPE group, then there would have been significant LI in the electrolytic lesion.

**TABLE 1**

**Experimental Effects on Drinking Behavior: Time to Complete 25 Licks Preceding CS Presentation (Pre-CS Period) and Total Number of Licks**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-CS latency ± SE</th>
<th>Total licks ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham–PE</td>
<td>3.85 ± 0.42</td>
<td>2752.6 ± 201.9</td>
</tr>
<tr>
<td>Sham–NPE</td>
<td>6.02 ± 1.48</td>
<td>2027.1 ± 277.9</td>
</tr>
<tr>
<td>Electro–PE</td>
<td>5.28 ± 1.78</td>
<td>2192.1 ± 268.7</td>
</tr>
<tr>
<td>Electro–NPE</td>
<td>6.73 ± 2.83</td>
<td>2267.9 ± 334.9</td>
</tr>
<tr>
<td>ANOVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>( F(1, 38) = 1.06 )</td>
<td>( F(1, 38) = 1.45 )</td>
</tr>
<tr>
<td>L</td>
<td>( F(1, 38) = 0.37 )</td>
<td>( F(1, 38) = 0.35 )</td>
</tr>
<tr>
<td>( L \times E )</td>
<td>( F(1, 38) = 0.04 )</td>
<td>( F(1, 38) = 2.20 )</td>
</tr>
<tr>
<td><strong>Experiment 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham–PE</td>
<td>10.67 ± 5.04</td>
<td>1592.3 ± 182.2</td>
</tr>
<tr>
<td>Sham–NPE</td>
<td>10.55 ± 4.48</td>
<td>994.5 ± 250.6</td>
</tr>
<tr>
<td>VEH–PE</td>
<td>3.90 ± 0.30</td>
<td>1991.6 ± 316.2</td>
</tr>
<tr>
<td>VEH–NPE</td>
<td>3.97 ± 1.41</td>
<td>616.0 ± 226.3</td>
</tr>
<tr>
<td>NMDA-PE</td>
<td>11.82 ± 7.02</td>
<td>1247.5 ± 255.3</td>
</tr>
<tr>
<td>NMDA-NPE</td>
<td>3.29 ± 0.17</td>
<td>1020.3 ± 292.9</td>
</tr>
<tr>
<td>ANOVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>( F(1, 35) = 0.48 )</td>
<td>( F(1, 35) = 10.72 )</td>
</tr>
<tr>
<td>L</td>
<td>( F(2, 35) = 0.76 )</td>
<td>( F(2, 35) = 0.28 )</td>
</tr>
<tr>
<td>( L \times E )</td>
<td>( F(2, 35) = 0.54 )</td>
<td>( F(2, 35) = 2.29 )</td>
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</table>

**Note.** Mean times (± SEM, SE) to complete 25 licks preceding CS presentation (pre-CS period) are expressed in seconds. Total licks (± SEM, SE) are the mean number of licks during the whole test session, before and after stimulus presentation. ns per cell given in text (10–12 in Experiment 1; 5–10 in Experiment 2). Groups: PE, preexposed; NPE, nonpreexposed; Sham, sham control; Electro, electrolytic lesion; VEH, vehicle-treated control for NMDA groups; NMDA, NMDA-treated. Data were analyzed by ANOVA (main effects: E, Exposure; L, Lesion; interaction: \( L \times E \), Lesion × Exposure).
group, as comparison between Electro–PE and Sham–NPE groups reveals (see Fig. 5). Does this imply that the apparent lack of LI resulted simply from lesion-induced disinhibition? Our results clearly suggest that this is not the case. Not only was there no evidence of disinhibition in the Electro–PE group, but in fact the rats in this group licked less than the rats in the Sham–PE group in almost every Bin, although this tendency was not statistically significant. Had there been no lesion-induced increase in suppression in the Electro–PE group, then in this case too there would have been significant LI within the electrolytic lesion group, as comparison between the Electro–NPE and the Sham–PE groups reveals (see Fig. 5). So the lack of LI in this experiment depends upon the lesion affecting conditioned suppression in two different directions, depending on preexposure condition. We have recently shown that aspiration lesions in ventral hippocampus similarly disinhibit licking in

FIG. 5. The number of licks made during each 1-min Bin in Exp. 1 by rats following sham operations or electrolytic nucleus accumbens lesions, after preexposure to the signal for shock or no preexposure to the signal for shock. The error bar shows 2 standard errors for between-group comparisons, taken from the significant 3-way interaction in the ANOVA.

FIG. 6. The number of licks made during each 1-min Bin in Exp. 2 by rats following sham operations, vehicle injections, or NMDA injections, after preexposure to the signal for shock or no preexposure to the signal for shock. The error bars show 2 standard errors for between-group comparisons, taken from the significant 3-way interaction in the ANOVA.
NPE rats in the drinkometer LI paradigm; however, in contrast to the present experiment, these lesions disinhibited licking in the PE rats to an equivalent extent, thereby leaving LI intact in the lesion group (Clark, Feldon, & Rawlins, 1992). Therefore, disinhibition as such, whether caused by changes in (the expression of) conditioning, motivation, or shock sensitivity, should not abolish LI, unless the rats are so totally disinhibited as to leave no room for a difference in licking rates between PE and NPE groups. Inspection of Fig. 5 makes it clear that there was ample room for an increase in licking in the Electro–PE group, since these rats licked less rapidly than controls and had a maximum licking rate that never attained that shown by the Electro–NPE rats over Bins 3–6. We therefore conclude that the electrolytic lesion abolished LI as such, as well as producing disinhibition in the Electro–NPE group.

As to the significant reversal of LI shown by the Electro group later in testing (Fig. 5), it is difficult to attach any theoretical significance to it because the effects appeared only relatively late in testing (in Bins 6 and 7), by which time the PE rats had made over 800 licks and nonsystematic variations in performance might be expected to appear. The onset of satiety complicates interpretation of the extinction measure of LI provided by the later Bins. The apparent reversal of LI in the Electro group should therefore be treated with caution.

The results obtained with the electrolytic N. Acc. lesion are thus consistent with the view that N. Acc. is part of the neural substrate of LI (Solomon & Staton, 1982). Our results therefore strengthen the models proposed by Weiner (1990) and Gray et al. (1991), which hold that the nucleus accumbens is a "final common path" for treatments abolishing LI. However, the effects of the electrolytic lesion might have resulted not from damage to the N. Acc. itself, but rather from damage to axons en passage through the area. The lesions that we made, located at the base of the lateral septum, might have severed axons projecting to or from the otherwise intact septum. Damage to fibers en passage through the septal nuclei has been held to account for effects that conventional septal lesions have upon the partial reinforcement extinction effect (Henke, 1974, 1977), which are not shared by excitotoxic septal lesions (Coffey, Feldon, Mitchell, Sinden, Gray, & Rawlins, 1989). Moreover, conventional total septal lesions or conventional lesions restricted to the dorsolateral septum produce disinhibition of conditioned suppression (Dickinson, 1975; Feldon, Rawlins, & Gray, 1982; Graeff & Rawlins, 1980); thus, our electrolytic lesions might have affected conditioned suppression performance in the present task by partially disconnecting inputs to or outputs from the dorsolateral septum. It was thus important to exclude the possible contribution that such fiber disruption might have made to the effects seen following our electrolytic N. Acc. lesions.

The demonstration, in Experiment 2, that it is possible to abolish LI by making N. Acc. lesions using the axon-sparing excitotoxin NMDA (Winn, 1991) indicates that the critical locus of this effect that we observed lay in the N. Acc. itself. This cytotoxic lesion exerted its effects through a change in the NMDA–PE group only. However, because the rats in all of the NPE groups showed very substantial suppression of licking (see Fig. 6), the possibility arises that the highly significant loss of LI in the NMDA lesion group reflected no more than a massive increase in suppression (as opposed to the decrease in suppression seen with the conventional lesion). However, inspection of Fig. 6 shows that, graphically speaking, the most complete suppression was in the VEH–NPE group, and yet the VEH group showed the greatest degree of LI, because the VEH–PE group showed the greatest degree of disinhibition as a result of preexposure to the CS. The Sham–NPE group and the NMDA–NPE group showed almost identical degrees of suppression, and yet preexposure led to disinhibition of licking (and, therefore, to LI) in the Sham–PE while failing to affect the NMDA–PE group (which therefore showed no LI). Overall, there was no evidence that the suppression of licking in the NPE groups was so great as to "prevent" the appearance of LI through the PE groups. We therefore conclude that the absence of LI in the NMDA lesion groups reflected primarily a lesion-induced effect on LI. In contrast, the lack of any sign of disinhibition in either NMDA lesion group indicates that the electrolytic lesion used in Experiment 1 must indeed have caused additional damage over and above the restricted loss of N. Acc. cell bodies induced by NMDA injection. The most parsimonious account of this aspect of the electrolytic lesion's effects would be to attribute the disinhibition to damage to fibers running to or from the lateral septum (see discussion of Experiment 1, above). The alternative is to assume that the electrolytic lesion produces more extensive damage within the N. Acc. itself (although our histology is not clear-cut on this point) and then to attribute the disinhibition to this increased lesion size. But this would mean that N. Acc. lesions duplicate the effects of lesions to the adjacent lateral
septum, and there is no statistical evidence of any disinhibition in the NMDA lesion group.

We therefore conclude that the N. Acc. plays a critical role in the normal development of LI, since even very restricted damage confined to cell bodies in the shell region is sufficient to abolish LI. The graphical enhancement of LI in the vehicle control groups even raises the intriguing possibility that a vehicle injection into N. Acc. might have long-lasting effects on the development of LI.

It is interesting to compare the results of Experiment 2 (using NMDA lesions) with those of Solomon and Staton (1982), who earlier suggested a key role for the N. Acc. in the development of LI. They showed that microinjection of d-amphetamine into N. Acc. attenuated LI. It therefore seems that both increasing dopamine activity (by injecting d-amphetamine) and the cell loss induced by excitotoxic (NMDA) lesions in N. Acc. have the same effects on LI. The dopaminergic projections from A10 to N. Acc. terminate on Spiny I cells, which themselves comprise 96% of the neurons in N. Acc. and are the main output neurons from N. Acc. (Groves, 1983; Swerdlow & Koob, 1987). Our findings suggest that the dopaminergic input to the N. Acc. is inhibitory, rather than excitatory; enhanced dopamine activity would thus have the same effect as eliminating the output from N. Acc. and would therefore produce effects resembling those of lesions. There has been considerable controversy about the actions of dopamine in the striatum (Groves, 1983); our results provide behavioral evidence supporting an inhibitory role for dopamine in the N. Acc., as originally suggested by Solomon and Staton (1982) and by Gray et al. (1991).

These conclusions do, however, conflict with a recent report that microinjection of d-amphetamine into N. Acc. did not abolish or attenuate LI (Killcross & Robbins, 1993). We think it would be premature to accept this negative conclusion. A negative conclusion from an experiment of this kind requires comparison with an unoperated control group. The only comparison groups included in the critical drug microinjection experiments were vehicle controls; this control group is certainly necessary if a positive drug effect is to be claimed. This is because the microinjection procedure might itself affect task performance and give rise to an apparent drug effect even if the drug itself has no real consequences. The drug's effects would thus be overestimated. However, for precisely the same reason, if a negative drug effect is to be claimed, then an additional comparison group is required in which the target structure has not been directly manip-

ulated. This is again because the microinjection procedure itself might affect task performance to yield an effect that resembles that of the drug. This would lead to an underestimate of the drug's true effects, even if the drug itself does have real consequences. It is logically insufficient to demonstrate only that there is no difference between a vehicle microinjection group and a drug microinjection group and to base the claim that there is no drug effect on this lack of a difference. At this point, therefore, we should reserve judgement as to possible discrepancies between our findings and theirs.

Gray et al. (1991) proposed that dysfunction of the subiculo-accumbens pathway (which terminates on the same accumbens cells that receive the mesolimbic dopamine input) leads to a functional dopamine overactivity in the N. Acc., which itself leads to a failure of normal attentional learning. Weiner (1990) suggests that the abolition of LI reflects enhanced behavioral switching rather than an inability to ignore irrelevant stimuli, but focuses on the same anatomical substrate. It is worth noting that the medial portion of the N. Acc. which our lesions destroyed has a particularly high density of D1 receptors (Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990), which may be the most critical subset of dopamine receptors underlying the antipsychotic action of the neuroleptics. Our results add support to this notion by identifying the same brain region as critical for the normal development of LI in rats, a capacity that is now known to be absent in acute schizophrenic patients.

Further specification of the nature of the deficit underlying the loss of LI may be possible when the theoretical interpretation of LI is clearer (e.g., Bouton, 1993; Mackintosh, 1975; Weiner, 1990). Such developments may in turn have implications for theories of information processing in schizophrenia.

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