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Recovery of Associative Function Following Early Amygdala Lesions in Rats

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Adult rats with amygdala lesions made at either Postnatal Day (PND) 10 or PND40 were tested on a series of reversal tasks that tap the ability to form stimulus–reward associations. PND40 rats were significantly impaired relative to both controls and PND10 rats on learning rate of the original discrimination and subsequent reversals. Analyses of discrete learning phases revealed that the impairment was specific to the postchance phase. The PND10 group was not impaired relative to controls on any measure. These results confirm prior findings that amygdala lesions sustained in adulthood impair the formation of stimulus–reward associations. They also demonstrate that substantial sparing or recovery of function is possible when the lesion is made during early development. Furthermore, the findings support the view that behavioral recovery may be more likely if the lesion is sustained near the time of peak synaptogenesis.

Over the last 20 years, many groups have explored the mechanisms underlying neural plasticity after peripheral or central nervous system (CNS) injury (Garraghty & Kaas, 1992; Kaas, 1999). This work suggests that two major classes of mechanism underlie cortical and subcortical plasticity: (a) morphological changes such as axonal and dendritic sprouting and synaptogenesis (Kolb, 1995); and (b) functional changes such as the reweighting of old connections within an existing network and the unmasking of previously "silent" synapses (Garraghty & Kaas, 1992; Gilbert, 1998; Kaas, 1999; Weiller, 1998). These changes are most widely seen after major CNS damage, in which nearly global reorganization occurs under some circumstances.

Although some brain circuits do undergo morphological changes after adult lesions (Aisaka et al., 1999; Darian-Smith & Gilbert, 1994; Pons et al., 1991), a growing body of research indicates that the greatest morphological reorganization occurs after brain damage incurred during the peak of synaptogenesis (Kolb, 1995). In rats, this peak occurs early in postnatal life (Kolb, 1995). Multiple previous studies demonstrated that rats recovered more substantially from frontal cortical damage sustained between postnatal day (PND) 7 and PND10 than from the same lesions made before that window or in adulthood (reviewed in Kolb, 1990). Specifically, lesions made before PND7 in the medial frontal cortex (Kolb, Petrie, & Cioe, 1996; Kolb & Whishaw, 1985), the posterior parietal cortex (Kolb, Holmes, & Whishaw, 1987), and the total frontal cortex (Kolb, 1987) result in significantly less sparing of behavioral function (compared with adult injury) than similar lesions made at PND9 or 10 (Kolb, 1987; Kolb et al., 1996; Kolb, Sutherland, & Whishaw, 1983). Kolb, Gibb, Gorny, and Whishaw (1998) also found that a lesion cavity produced at PND10 subsequently became filled with neural tissue, a phenomenon not observed with lesions produced at earlier and later ages. Furthermore, whereas adult-lesioned animals exhibited an increase in dendritic branching only in the perilesional area, animals lesioned on PND10 had more branching throughout the damaged hemisphere (Kolb & Gibb, 1991, 1993; Kolb & Sutherland, 1992). Although some morphological change accompanies adult brain damage, structural reorganization is possible to a much greater extent after early lesions.

In contrast to structural reorganization, functional reorganization can be widespread over most of the life span (e.g., Weiller, 1998). One major mechanism of functional reorganization is the unmasking of previously inhibited synapses (Garraghty & Kaas, 1992; Kaas, 1999). For example, during lidocaine application to the facial skin in adult rats, immediate and major changes occur in receptive fields of neurons in the thalamic nucleus ventral posteromedial thalamic nucleus (Krupa, Ghazanfar, & Nicolelis, 1999; Nicolelis, Lin, Woodward, & Chapin, 1993). Those neurons appear to become responsive to new portions of the sensory space as a result of the anesthetic-induced disinhibition of previously inhibited connections (Kaas, 1999). Neuroimaging studies in humans suggest that similar functional mechanisms permit a partial recovery of function in both adults and children with CNS injuries. These studies suggest that connections within an existing network are reweighted to shift the processing burden to circuits with inputs

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and outputs similar to those of the damaged region (Seitz et al., 1998; Weiller, 1998).

Most of the foregoing studies, particularly those measuring morphological changes, involved cortical lesions. Relatively few groups examined the long-term consequences of subcortical lesions made at the peak of synaptogenesis relative to other time periods. It is, therefore, uncertain whether similar recovery of function can occur after damage to subcortical areas at this particular developmental period. To address this issue, we tested whether greater recovery or sparing of behavioral function occurs after amygdala lesions made on PND10, during the period of high synaptogenesis (Kolb, 1995), relative to rats lesioned on PND40, after the period of high synaptogenesis. The amygdala was chosen for several reasons. First, it plays a critical role in a number of well-defined adult behaviors. Second, there is controversy over whether one major function of the amygdala, the formation of associations between neutral stimuli and their affective value, shows recovery of function after early lesions. Finally, amygdala pathology is prominent in a number of neurological disorders affecting children, suggesting that early damage to this structure may be of clinical significance.

The amygdala comprises a heterogeneous group of nuclei whose input and output pathways render it uniquely suited to play a critical role in the integration of cognitive and emotional information (Swanson & Petrovich, 1998). The amygdala, particularly the basolateral and lateral nucleus complex, is thought to be critical for the formation of associations between primary reinforcement and discrete stimuli that have no intrinsic value of their own (Gaffan, 1992; LeDoux, 1995). In support of this hypothesis, amygdala lesions made in adult primates or rodents impair the animals on tasks in which stimuli must be associated with their affective value to guide behavior (Cador, Robbins, & Everitt, 1989; Eleftheriou, Elias, & Norman, 1972; Gaffan & Harrison, 1987; Everitt, Cador, & Robbins, 1989; Everitt, Morris, O'Brien, & Robbins, 1991; Hiroi & White, 1991; Jones & Mishkin, 1972; Kentridge, Shaw, & Aggleton, 1991; McDonald & White, 1993; Pribram, Douglas, & Pribram, 1969; Spevack & Pribram, 1973; Spiegler & Mishkin, 1981).

Relatively little information exists on whether this type of associative dysfunction also results from amygdala damage incurred early in postnatal development. Several studies of early amygdala damage did not assess the recovery of associative function in adult animals (Dicks, Myers, & Kling, 1969; Sananes & Campbell, 1989; Schuckman, Kling, & Orbach, 1969; Sullivan & Wilson, 1993). Unfortunately, those studies that did address this question presented conflicting conclusions. Thompson (1981) compared monkeys amygdalectomized in infancy versus adulthood on appetitively motivated delayed alternation and position discrimination reversal learning. When tested as adults, both groups were significantly and equally impaired on these tasks, suggesting that in some cases recovery of associative function does not occur after early amygdala lesions. In contrast, Molino (1975) tested adult rats that had been amygdalectomized at PND10 or PND60 on another instrumental, associative task of active avoidance. They found that only the rats lesioned at PND60 were impaired, suggesting significant recovery of function for this task in the early-lesioned rats.

The reasons for these disparate results are not clear. Species differences do not appear to be a likely mechanism. Numerous data suggest correspondence between rats and primates in terms of the amygdala's associative role as well as the mechanisms thought to underlie recovery of function (e.g., Sarter & Markowitsch, 1985; Xerri, Coq, Merzenich, & Jenkins, 1996). Alternatively, recovery potential may be determined by whether the task is appetitive or aversive. However, given the overall similarity in brain circuits mediating associative function for the two types of task (e.g., Hatfield, Han, Conley, Gallagher, & Holland, 1996), this explanation also seems unlikely. A final explanation that could reconcile the two sets of results concerns the timing of the infant lesions. The rats in the Molino study sustained amygdala lesions during the peak of synaptogenesis (Kolb, 1995), whereas the monkeys in the Thompson study sustained lesions slightly after that peak, although pruning to adult levels had not yet occurred (Granger, Tekaia, Le Sourd, Rakic, & Bourgeois, 1995). Thus, the results of the two studies may not be disparate but instead reflect the importance of the timing of the lesion relative to peak synaptogenesis.

Clarification of the circumstances under which sparing or recovery of function after early amygdala damage occurs has important clinical relevance, because amygdala pathology has been reported in several childhood neurological disorders. In addition to stemming from early traumatic brain injury, long-term amygdala dysfunction may result from childhood temporal lobe epilepsy (Pitkanen, Tuunanen, Kalviainen, Partanen, & Salmenpera, 1998) as well as from Urbach-Wiethe disease (Cinaz, Guvenir, & Gonlusen, 1993). Furthermore, early-onset schizophrenia (Jacobsen et al., 1996; Yeo et al., 1997) and autism (Nowell, Hackney, Muraki, & Coleman, 1990; Hoon & Reiss, 1992) have been linked to early amygdala pathology. Greater knowledge about recovery of function after early amygdala damage will aid in understanding the putative role of damage to this structure in these disorders.

The present investigation assessed the extent of recovery of function after bilateral lesions of the amygdala made on PND10 versus PND40. We predicted that rats lesioned on PND10 would show more recovery than those lesioned on PND40, similar to the results of Molino's (1975) study. In addition, to assess the generality of this earlier finding, we used appetitive rather than aversive tasks. Specifically, we used two- and three-choice olfactory serial reversal tasks. Serial reversal learning has been shown to be critically dependent on normal amygdala function, based on studies in which this structure was lesioned during adulthood (Eleftheriou et al., 1972; Jones & Mishkin, 1972; Kentridge et al., 1991; Pribram et al., 1969; Spevack & Pribram, 1973). Additionally, several other cortical and subcortical structures are known to play roles in learning such tasks, including the prelimbic and infralimbic regions of the prefrontal cortex (Jones & Mishkin, 1972; Ragozzino, Detrick, & Kesner, 1999), the dorsal striatum (Hart, Chaimas, Moore, & Stein, 1978; Kolb, 1977; Mitchell, Channell, & Hall, 1985; Sabel, Karden, & Stein, 1983), the ventral striatum (Taghzouti, Louilot, Herman, Le Moal, & Simon, 1985), the mediodorsal thalamic nucleus (McBride & Slotnick, 1997), and the basal forebrain cholinergic nuclei (Evenden et al., 1989). These areas might be expected to compensate for the amygdala loss (Weiller, 1998). Furthermore, all of these areas undergo a peak of synaptogenesis and pruning of synapses to near-adult levels before PND40 (e.g., for the frontal lobes, see Markus & Petit, 1987; for the striatum, see Uryu, Butler, & Chesselet, 1999). Based on these data, it is hypothesized that some recovery of function may occur after the adolescent lesions as a result of functional as well as

minor morphological reorganization. However, much greater recovery should occur after lesions at PND10 because of widespread morphological reorganization.

In the present study, in-depth analyses of discrete phases of the learning process were conducted in addition to analyses of overall learning rate. Serial reversal tasks are characterized by a progression of several phases of learning, each phase supported by different cognitive processes. These phases include (a) a period of initial perseverative responding to the previously correct cue, (b) a period of chance-level responding, and finally (c) a gradual associative phase during which the association between the reward and the new correct cue is mastered (Garavan, Morgan, Hermer-Vazquez, et al., 2000; Hilson & Strupp, 1997; Jones & Mishkin, 1972). Impaired reversal learning can result from disruption in one or more of these processes. For example, damage to prefrontal cortex impairs reversal learning rate as a result of increased perseverative responding to the previously correct cue, whereas amygdala damage impairs reversal learning because of associative dysfunction. These in-depth analyses allowed us to determine whether associative ability, specifically, exhibited recovery of function after early amygdala lesion.

Method

Subjects

Twenty female Long-Evans rats were obtained from Harlan Sprague Dawley (Indianapolis, IN). A male rat was placed into the cage with each female until a sperm plug was observed, after which the dams were housed singly in polycarbonate cages with wood chip bedding. At parturition, one female pup from each litter was assigned to each of four treatment groups: control (CTR), 10-day-old amygdala lesion (L10), 40-day-old amygdala lesion (L40), and lead exposed. (The results concerning lead exposure are not presented here.) The pups were then cross-fostered such that the resulting litters were composed of four pups in the same treatment group and four additional pups not used in the study. This fostering procedure was used to permit littermate comparisons for the four treatment groups, despite the fact that the lead-exposure regimen involved feeding the dam lead-adulterated water. All cross-fostering took place within 72 hr after birth.

At PND10, each pup in the L10 group received bilateral amygdala lesions. Also at PND10, half of the control litters received sham surgeries (CTR sham) consisting of a scalp incision comparable to that made during lesion surgery. However, no holes in the skull were drilled, and the skin was immediately resutured. These sham lesions controlled for (a) the administration of anesthesia followed by general trauma early in development and (b) the possibility of altered maternal behavior to pups having undergone surgery. At PND21, each pup was weaned and housed with another member of its treatment group in metal wire mesh hanging cages. The room in which the rats were kept and tested was maintained on a reversed light–dark cycle. Drinking water was available ad libitum. Food was available ad libitum until approximately 3 weeks before testing, at which time the rats were restricted to 18 g of lab chow per day. At PND40, all rats in the L40 group received bilateral amygdala lesions.

The original study was designed to include 8 CTR, 8 CTR-sham, 20 L10, and 12 L40 rats. During subsequent behavioral testing, one CTR rat was removed after failure to learn the first olfactory discrimination and was replaced with another CTR rat. Three rats were removed because of experimenter error: 1 CTR-sham rat was replaced with a CTR rat and 2 L10 rats were removed without replacement. The final numbers of subjects included in the study were 9 CTR, 7 CTR-sham, 18 L10, and 12 L40 rats.

Apparatus

Testing was conducted in 12 automated Plexiglas chambers as previously described in Hilson and Strupp (1997). Briefly, each chamber was enclosed in a sound-attenuating wooden box and controlled by an IBM XT clone. Each chamber comprised a square waiting area (26.5 × 25 × 30 cm) and a testing alcove (11.5 × 7.5 × 7.5 cm), separated by a guillotine-type metal door. Three funnel-shaped ports were mounted horizontally along the alcove wall facing the inside of the chamber with the left and right ports each at a 45° angle relative to the center port. The distance between the left and right ports was 8 cm. The scented air that served as the discriminative cues in this study was directed into the alcove at a rate of 1.0 L/min using a polyethylene tube connected to bottles containing liquid odorants located outside the testing chamber. The scented air was pumped through these ports using solenoid valves situated behind each testing chamber. A 1-s nose poke into one of the ports constituted a choice. A set of infrared phototransistors and a light source monitored the entrance to the alcove and each port. Correct responses were rewarded with a 45-mg Noyes food pellet delivered directly into the alcove.

Surgical Procedure

L10 group. Each rat pup (23–28 g) was anesthetized by inhalation of isoflurane (0.1–0.5%). A 2.5-cm incision was made along the top of the head, and the scalp was retracted to reveal the external acoustic meatus. The rat was then placed in a Stoelting 51625 neonatal stereotaxic adapter (Stoelting Instruments, Wood Dale, IL) attached to a Kopf 900 stereotaxic apparatus (Kopf Instruments, Tujunga, CA) such that the ear bars were inserted gently into each meatus. The rat was positioned such that bregma and lambda were level. Bilateral amygdala lesions were made electrolytically using a Grass model SD-S stimulator (Grass Instruments, Quincy, MA). This method of lesioning was selected instead of the more common excitotoxic procedures (such as ibotenic acid) following reports of ibotenate lethality in infant rats (M. Stanton, personal communication, April, 1997). A stainless steel electrode (FHC Inc., Bowdoinham, ME) with diameter of 250 μm insulated except for 400 μm at the tip was positioned at the following coordinates: bregma, −2.5 mm; lateral ±3.9 mm; ventral, −7.5 mm from the skull surface. For all lesions, 0.2 mA of current was passed for 50 s. The incision was sutured with cyanoacrylate, and the pup was given .05-ml penicillin subcutaneously. After recovery from anesthesia, the pup was returned to its litter.

L40 group. Each rat (142–189 g) was anesthetized with a combination of xylazine (10 mg/kg) and ketamine (75 mg/kg) and placed into the stereotaxic apparatus. The rat was positioned such that the bregma and lambda were level. Bilateral amygdala lesions were made as described previously at coordinates: bregma, −2.2 mm; lateral, ±4.3 mm; ventral, −9.1 mm from the skull surface. A 0.2-mA current was passed for 50 s. After each surgery, the incision was sutured as discussed previously, and the rat was given .05-ml Baytril (enrofloxacin) subcutaneously and allowed to recover. Once the rat was able to move about, it was returned to its home cage.

Histology and Lesion Assessment

At the conclusion of behavioral testing, all rats in both lesion groups were given an overdose of pentobarbital sodium and perfused transcardially with 0.1 M phosphate buffer followed by 4% formaldehyde. The brains were removed and postfixed in 4% formaldehyde solution. The next day the brains were sectioned at 50 μm on a vibratome. Every other section was collected and stained with cresyl violet for histological verification of lesion placement.

A complete set of lesion tracings, covering the full extent of each lesion in each hemisphere, was made for subgroups of approximately five rats in each lesion group. Two scorers, unaware of the treatment condition of the

rats, rated the extent of damage to several structures determined by a preliminary analysis to be most affected: the basolateral nucleus of the amygdala, the lateral nucleus of the amygdala, the central nucleus of the amygdala, the caudate and putamen, the globus pallidus, CA3 of the hippocampus, the stria terminalis, the substantia innominata, and the nucleus basalis of Meynert. The scorers assessed the damage in each hemisphere, separately for each rat. A score of 0 was given if there was no damage; a score of 1 was given if there was some damage but one third or more of the structure remained intact; and a score of 2 was given if there was extensive damage (i.e., less than one third of the structure remained).

Procedure

Behavioral testing began at 12 weeks of age for all rats with the exception of the 3 replacements that started at 13 weeks (1 subject) or 15 weeks (2 subjects) of age. Before the start of the discrimination tasks, each rat was trained to make a 1-s nose poke into the ports to receive a reward pellet. After nose-poke training, each rat was tested on a two-choice olfactory discrimination followed by three reversals of the original discrimination. At the conclusion of the two-choice serial reversal task, the rats were tested on a similar three-choice task series composed of an initial olfactory discrimination with four subsequent reversals. Throughout all training and testing, each rat received one session per day 6 days a week. Each session lasted for 150 min or 250 trials, whichever came first. All behavioral testing was conducted by individuals unaware of the treatment condition of the rats.

The following general procedure was used for each of the four two-choice tasks (original discrimination plus three reversals) and each of the five three-choice tasks (original learning plus four reversals). A trial was initiated by raising the alcove door, permitting the rat to enter the alcove. If the rat failed to enter the alcove within 60 s, the door was lowered and the trial scored as a nontrial. A trial in which the rat entered the alcove but failed to make a response within 60 s was also scored as a nontrial. Nontrials were not scored as incorrect and did not contribute to the 250-trial maximum per testing day. A 1-s nose poke into the funnel from which the correct odor emanated was rewarded with a pellet. Any response (correct or incorrect) terminated the odors. After the rat left the alcove, the door was lowered, signaling the end of the trial.

The discriminative cues for the two-choice olfactory tasks were anise- and almond-scented air and for the three-choice tasks strawberry-, rose-, and lilac-scented air. These cues were produced by forcing air through a liquid mixture of flavored extract (donated by McCormick, Hunt Valley, MD and R. T. French, Wayne, NJ) mixed with propylene glycol to a concentration of 0.1 g/ml. For the two-choice task series, the center port was covered with a metal plate to prevent the rat from making a response to this port, whereas for the three-choice tasks all three ports were available. At the onset of a trial, each of the different olfactory cues was presented simultaneously, one from each open port. The port from which each odor emanated on a given trial was determined by a pseudorandom sequence; the stipulations were that (a) the presentation of each odor from each funnel was balanced within a session, and (b) no odor could be presented from the same port more than four consecutive times. The air was cleared by fans mounted on the outside of the chambers at a rate of four exchanges per minute. Testing on the discrimination continued until the rat reached the learning criterion, defined as one session of at least 200 trials at 88% correct or higher. The correct odor for the initial discrimination of both the two- and three-choice task series was counterbalanced within and across treatment conditions.

Each rat was placed on a reversal of the initial discrimination on the session immediately after reaching the learning criterion. The odor that had been previously correct was now incorrect. A total of three reversals was administered for the two-choice task series, with the correct stimulus alternating with each new reversal. For the three-choice serial reversal task, four reversals were given, with the correct stimulus alternating among the three odors. Although the odor that was correct for the initial discrimination varied among rats (as defined previously), all rats followed the same sequence of correct odors for the five three-choice serial reversal task: Strawberry correct was always followed by rose, which was followed by lilac, which was followed by strawberry, and so on. The learning criterion for the reversals was the same as for the original discrimination.

Immediately after testing, each rat was given a daily allotment of food minus the weight of pellets consumed in the session. For each rat, the starting daily allotment was 18 g. If a rat failed to make 200 responses on two consecutive sessions, this amount was lowered by 1 g to increase the motivation to respond.

Data Analysis

A sequence of planned analyses was conducted to compare the performance of the different treatment groups. First, the groups were compared on overall learning rate (the total number of errors to criterion for each task). Next, we conducted in-depth analyses to compare the groups on the specific phases that comprise reversal learning: (a) perseveration to the previously correct odor, (b) chance levels of responding, and (c) a phase of gradually learning to respond consistently to the new correct odor until criterion was reached. For each subject, performance on all tasks was first smoothed by calculating moving averages of percentage correct, using bins of 30 trials (nontrials were first discarded). Bins moved in one-trial increments, such that the first bin contained Trials 1 to 30, the second bin Trials 2 to 31, and so on. The length of each phase (in trials) was determined as follows: The perseverative phase consisted of trials from the beginning of a reversal until the trial at which the moving average was not statistically different from chance levels (36% for the two-choice task and 21% for the three-choice task). The chance phase consisted of trials from the end of the perseverative phase until the trial at which the moving average was significantly above chance (63% for the two-choice task and 46% for the three-choice task). For the two-choice tasks, the postchance phase consisted of trials from the end of the chance phase until the trial at which the moving average reached criterion (88%). For the three-choice tasks, the postchance phase was divided into two subphases: an early postchance phase (46–66%) and a late postchance phase (66–88%). Finally, for each subject, we analyzed an end phase consisting of the trials between the first bin at or above 88% and the time at which the rat reached criterion (one session of 200 trials or more at 88% or higher).

A separate mixed-model analysis of variance (ANOVA) was conducted for each dependent measure in the analysis with PROC MIXED (SAS Institute, 1990); fixed factors included treatment, reversal, and problem, and random factors included rat and box.

Analyses were also conducted on body weight, alcove latency, and lesion size. An ANOVA with the fixed factor treatment and with the random factor rat was conducted on the rats' mean body weight across testing. For alcove latency, a mixed-factor ANOVA was run on rats' mean alcove latency for original learning and each reversal, with fixed factors treatment, reversal, and odor and random factors rat and box. These two analyses also used PROC MIXED. Finally, for the lesions, unpaired t tests were used to compare the severity of damage to each structure bilaterally across the two lesion groups. To construct this dependent measure, the ratings for each lesion from each scorer were first averaged. These scores never differed by more than one point. Then bilateral lesion scores were constructed as follows: If the score for a given rat was greater than 0 in both hemispheres, then those two scores were averaged. However, if the rat sustained no damage to that structure on one or both sides of its brain, its (bilateral lesion extent) score was 0. Unpaired t tests were conducted for the two lesion treatment groups with this dependent measure, using PROC TTEST in the version of SAS described previously.

Results

Histology

Figure 1A and B show representative lesion reconstructions from the L10 and L40 groups, respectively. Representative photomicrographs of the L10 and L40 groups are shown in Figure 2A and 2B respectively. Most rats in both lesion groups sustained considerable, although incomplete, damage to the amygdala. Lesions in the L10 group frequently included damage to the central, basolateral, and lateral nuclei of the amygdala. Lesions in the L40 group included damage predominantly to the central and basolateral nuclei, with somewhat less consistent damage to the lateral nucleus. In both groups, several subjects also sustained considerable damage to the basomedial and medial nuclei. In addition to damage confined to the amygdala, many subjects from both groups sustained some damage to the caudate nucleus, globus pallidus, CA3 of the hippocampus, and the stria terminalis. A few subjects in each group also had damage to the basal forebrain, including the nucleus basalis of Meynert.

We used *t*-tests to compare the bilateral extent of lesions in the L10 versus L40 rats. Although the groups did not differ in the extent of damage to the central nucleus of the amygdala ($p > .45$), the L10 group sustained more damage to their basolateral, $t(28) = 2.427$, $p = .022$, and lateral, $t(28) = 2.296$, $p = .029$, nuclei. For most of the collateral structures rated, the L10 and L40 groups sustained comparable bilateral damage (all $ps > .45$). However, the L10 group received considerably more damage to CA3 and the fimbria of the fornix, $t(28) = 3.126$, $p = .004$. The possible behavioral consequences of this greater damage are discussed further in the *Initial Acquisition and Reversal Learning* and Discussion sections.

Body weight. The mean body weights for the L40, L10, and CTR rats were 232 g, 245 g, and 243 g, respectively. These differences were not statistically significant, $F(2, 42) = 2.04$, $p =$

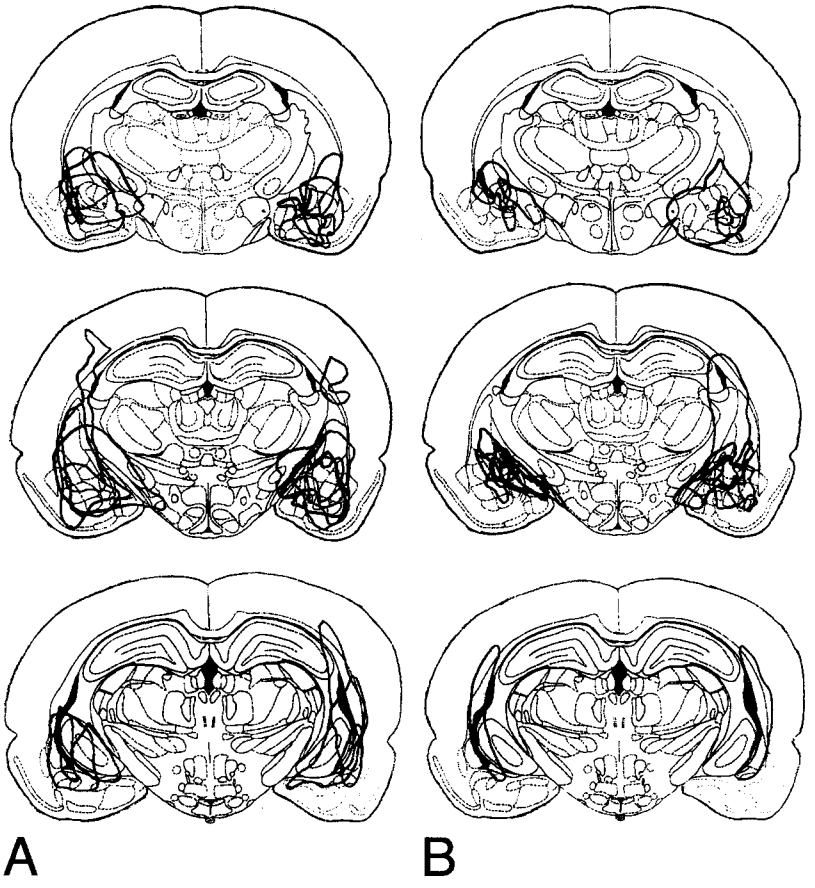

Figure 1. Lesions for 5 representative rats from each lesion group at three different anterior–posterior levels of the brain. A: 10-day-old amygdala lesion rats. B: 40-day-old amygdala lesion rats. The top images are at bregma −2.12 mm; the middle images, bregma −3.14 mm; and the bottom images, bregma −4.16 mm. Note the collateral caudate–putamen damage visible in the middle images especially and the collateral CA3 damage visible in the bottom images especially. "Representative" rats were chosen from groups of 4 or 5 rats per lesion tracing page, with a fairly typical set of 5 rats (i.e., some with well-made lesions and others with more poorly made lesions), selected from each lesion age group. From *The Rat Brain in Stereotaxic Coordinates* (2nd ed., Figures 26, 30, and 34) by G. Paxinos and C. Watson, 1986, New York: Academic Press. Copyright 1986 by Academic Press. Adapted with permission.

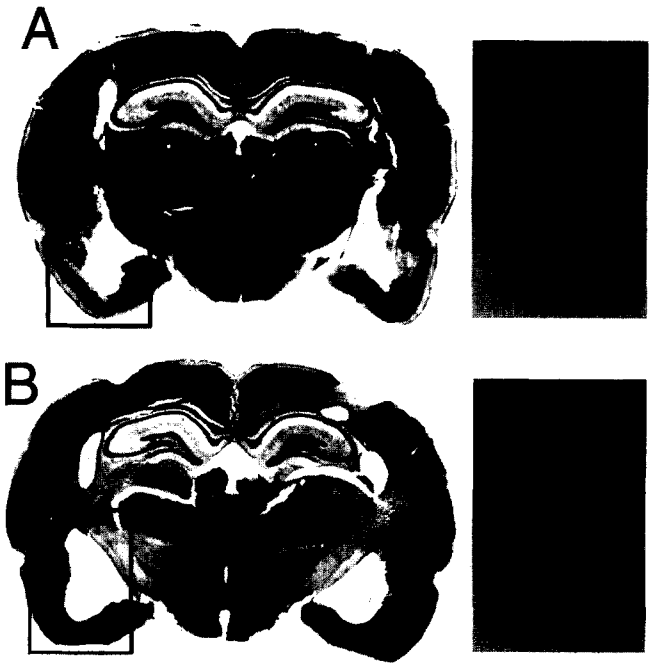

Figure 2. Lesion cavities in brains that sustained bilateral electrolytic amygdala lesions. A: Lesions sustained at Postnatal Day (PND) 10. B: Lesions sustained at PND40. Lesion area shown enlarged at right. All rats were killed by overdose in adulthood.

.14. In addition, there were no treatment differences in the mean daily food allotments, $F(2, 41) = .84, p > .40$, despite the need to make adjustments on an individual basis.

Alcove latency. Alcove latency was analyzed as an index of motivation to perform the task. This measure was defined as the time between opening of the alcove door at trial onset and the entry of the rat into the alcove. For the two-choice tasks, ANOVA did not reveal a treatment effect ($p > .60$) but a marginally significant Treatment × Task interaction, $F(6, 265) = 2.10, p = .0536$. However, subsequent contrasts did not reveal significant treatment differences on any reversal. Similarly, for the three-choice task series, ANOVA did not reveal a treatment difference ($p > .60$) but a significant Treatment × Task interaction, $F(8, 323) = 2.17, p = .0291$. However, again, contrasts did not reveal a significant treatment effect for any reversal. These findings argue against group differences in motivation to solve the task.

Initial Acquisition and Reversal Learning

Analysis of errors to criterion for the two-choice task. The data required a $\log_{10}$ transformation to attain a normal distribution. Because an initial analysis did not reveal significant differences between the two control groups in overall learning rate ($p > .50$), they were combined for further analyses. An analysis including all four tasks (original learning and three reversals) revealed evidence suggestive of a treatment effect, $F(2, 28.6) = 2.83, p = .1169$; the L40 group tended to make more errors than either the L10 group or the control groups (Figure 3). There was also a significant main effect of reversal, $F(3, 152) = 17.71, p < .0001$; initial learning (Reversal 0) was the easiest, the first reversal the hardest, and the subsequent reversals progressively easier. Additionally, there was a significant Treatment × Reversal effect, $F(6, 84.7) = 3.09, p = .009$. Contrasts were used to understand the nature of this interaction (Snedecor & Cochran, 1989). These tests revealed that there was no difference between the treatment groups on original learning and the second reversal (all $ps > .50$). In contrast, on the first reversal, the L40 group performed marginally worse than the CTR rats ($p = .1005$) and significantly worse than the L10 group ($p = .005$). Similarly, on the third reversal, the L40 group was impaired relative to CTR rats ($p = .0025$) and the L10 group ($p = .0145$). The L10 group did not differ from the CTR rats on any of these measures ($ps > .20$).

Analysis of errors to criterion for the three-choice task. The data required a $\log_{10}$ transformation to attain a normal distribution. Again, because an initial ANOVA did not reveal differences between the CTR and CTR-sham rats ($p > .50$), these groups were combined for further analysis. An ANOVA revealed significant main effects of treatment, $F(2, 25.1) = 5.69, p = .0092$, and reversal, $F(4, 37.7) = 10.64, p = .0001$. The interaction of treatment and reversal was not significant. Contrasts revealed that the reversal effect resulted from the second reversal, which was the most difficult for all treatment groups (Figure 4). Contrasts also revealed that the L40 rats were impaired on all reversals, committing significantly more errors than CTR rats, $t(24.7) = -2.56, p = .0169$, and L10 rats, $t(24.4) = -3.24, p = .0035$. The L10 rats did not differ from CTR rats ($p > .55$).

Analysis of specific phases of the reversal learning process for the two-choice task. The data required a $\log_{10}$ transformation to attain a normal distribution. A preliminary analysis revealed that the control groups did not differ significantly on any factor included in the analysis and could be combined ($p > .30$). The results of a subsequent ANOVA, with the three reversals included, revealed significant main effects for reversal, $F(3, 31.5) = 17.53, p < .0001$, and phase, $F(3, 33.2) = 246.53, p < .0001$, and significant interactions between treatment and reversal, $F(6, 447) = 2.53, p = .02$, and treatment and phase, $F(6, 527) = 2.15, p = .045$. The reversal effect derived from the first reversal being

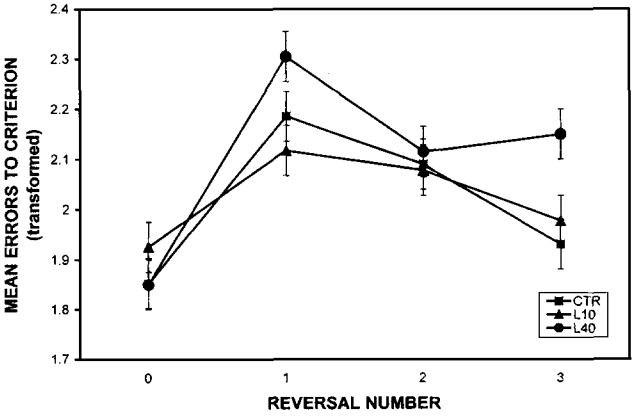

Figure 3. Mean (±*SEM*) number of errors to attain criterion in the two-choice task series. The original discrimination is referred to as Reversal 0, followed by Reversals 1 to 3. Treatment groups are controls (CTR) and rats with amygdala lesions at Postnatal Day (PND) 10 (L10) and PND40 (L40).

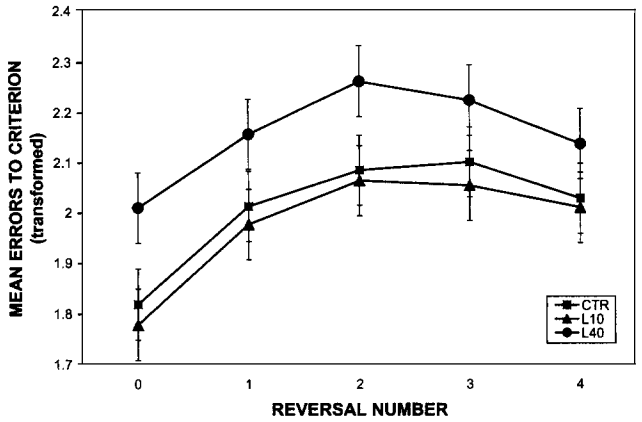

Figure 4. Mean (±*SEM*) number of errors to attain criterion in the three-choice task series. The original discrimination is referred to as Reversal 0, followed by Reversals 1 to 4. Treatment groups are controls (CTR) and rats with amygdala lesions at Postnatal Day (PND) 10 (L10) and PND40 (L40).

the most difficult and subsequent reversals becoming easier. The phase effect was due to a progressive increase in the duration (number of trials) of the phases.

Contrasts were performed to determine the loci of the Treatment × Phase interaction. These analyses revealed that the duration of the perseverative phase was not altered by the 10-day lesion ($p > .95$) or 40-day lesion ($p > .50$) relative to CTR rats (Figure 5). Furthermore, there was no difference between the two lesion groups ($p > .45$). In contrast, the chance phase was significantly shorter for the L10 group than for CTR rats ($p = .008$), a trend that was also seen for the L40 rats relative to CTR rats ($p = .079$). Again, the two lesion groups did not differ from each other ($p > .45$). In addition, the L40 rats exhibited a significantly longer postchance learning phase than the CTR rats ($p = .039$). The L10 group, however, did not differ significantly from CTR rats ($p > .35$) or the L40 group ($p > .20$). None of the treatment groups differed in the length of the end phase (all $ps > .20$).

Analysis of specific phases of the reversal learning process for the three-choice task. The data required a $\log_{10}$ transformation to attain a normal distribution. Again, CTR rats did not differ significantly ($ps > .30$) and were combined. The results of an ANOVA including the four reversals revealed a significant main effect of treatment, $F(2, 30.7) = 4.18$, $p = .0249$, reversal, $F(4, 43.7) = 9.79$, $p = .0001$, and phase, $F(4, 45.2) = 385.08$, $p < .0001$, and significant interactions between treatment and phase, $F(8, 847) = 2.00$, $p = .0437$, and reversal and phase, $F(16, 823) = 4.78$, $p = .0001$ (Figure 6). Contrasts were conducted to understand the interaction of treatment and phase. The duration of the perseverative phase did not differ between the treatment groups (all $ps > .70$). In contrast, the length of the chance phase was significantly shorter for the L10 rats than for CTR rats ($p = .0041$). The L40 group did not differ from CTR rats in the duration of this phase ($p > .90$). The early postchance phase (46–66%) was significantly longer for L40 rats than for CTR ($p = .0052$) and L10 ($p = .0013$) rats. The duration of this phase was not different for the CTR and L10 rats ($p > .75$). The late postchance phase (67–88% correct) showed a similar pattern; the L10 rats did not differ from CTR rats ($p > .90$), and the L40 group required marginally more trials to complete this phase than both the CTR ($p = .0990$) and the L10 ($p = .0656$) rats. Finally, the treatment groups did not differ in the duration of the end phase (all $ps > .25$).

Discussion

The results of this study demonstrate that the behavioral consequences of near-total amygdala destruction depend on the age at which the damage occurs. On the basis of analyses of overall learning rate (errors to criterion), the L40 rats were significantly impaired relative to CTR rats on tests of serial reversal learning. In the two-choice tasks, the L40 group was impaired on two of the three reversals but did not show a deficit on the original discrimination. In the three-choice tasks, this group was impaired on the original learning as well as all reversals. In sharp contrast, the

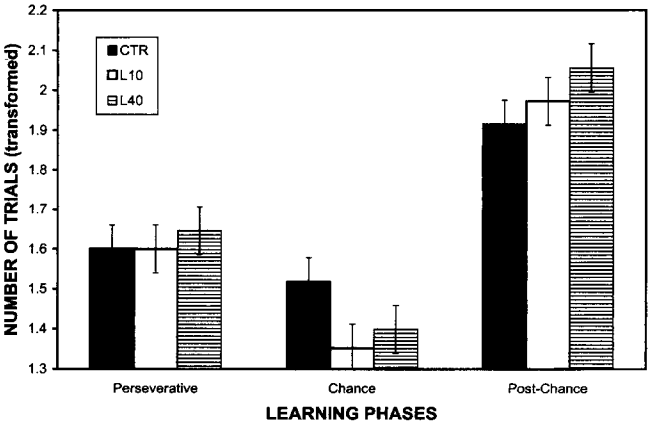

Figure 5. Mean (±*SEM*) number of trials comprising different phases of reversal learning in the two-choice tasks (all four tasks combined). Treatment groups are controls (CTR) and rats with amygdala lesions at Postnatal Day (PND) 10 (L10) and PND40 (L40).

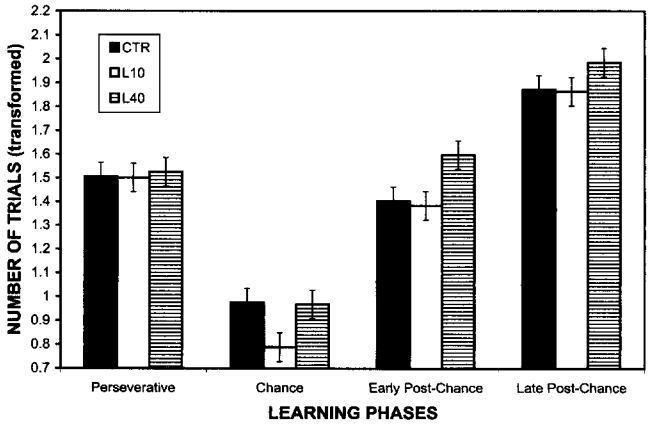

Figure 6. Mean (±*SEM*) number of trials comprising different phases of reversal learning in the three-choice tasks (all five tasks combined). Treatment groups are controls (CTR) and rats with amygdala lesions at Postnatal Day (PND) 10 (L10) and PND40 (L40).

group lesioned at PND10 did not differ from CTR rats in learning rate on any of these tasks.

A more in-depth analysis examining specific phases of the learning process shed light on the nature of the learning deficit in the L40 group and uncovered behavioral alterations in the L10 group despite their normal overall learning rate. The specificity of the impairment in the L40 group strongly implicates associative dysfunction. These rats were impaired only during the postchance learning phase, a phase characterized by the development of an association between the new correct stimulus and reward. In contrast, the L40 group did not exhibit a lengthening of the initial period of perseverative responding to the previously correct cue, arguing against deficient inhibitory control or behavioral–cognitive inflexibility as the cause of the deficit. Additionally, they were not impaired in the end phase, a period presumably beyond the point at which the new stimulus–reward association is formed. The absence of impairment in this last phase, coupled with the normal learning rate seen in the initial two-choice discrimination, rules out various nonspecific performance factors (e.g., decreased motivation, impaired sensory acuity) as the cause of the dysfunction. In addition, the absence of treatment differences in alcove latency provides converging evidence that motivational differences cannot account for the observed learning impairment of the L40 group. Instead, this pattern across phases suggests that the impairment of the L40 group lies specifically in the ability to form new links between the correct stimulus and reinforcement. In contrast, the rats lesioned at PND10 were entirely normal in the rate at which they learned the new association, as evinced by the normal duration of the postchance phases of both the two- and three-choice task series. These data demonstrate that near-complete sparing or recovery of this associative function is possible if the lesion is sustained at PND10.

These in-depth analyses also uncovered the unexpected finding that the L10 group exhibited a chance phase that was significantly shorter than controls for both the two- and three-choice task series. The group lesioned at PND40 exhibited a trend toward this effect for the two-choice but not the three-choice task. Neither the neural nor the cognitive basis of this effect is known. With respect to the first of these issues, it is unknown whether this effect reflects damage to the amygdala or some collateral structure (as mentioned, the L10 group did sustain more collateral damage than the L40 group) or whether it is an artifact of the extraamygdaloid changes that occurred secondary to the lesion (Kolb, 1995). This finding has not been demonstrated by previous studies of amygdala lesion and reversal learning (Aggleton & Passingham, 1981; Douglas & Pribram, 1966; Jones & Mishkin, 1972; Pribram et al., 1969; Spevack & Pribram, 1973).

The cognitive basis of this shortened chance phase is also unknown. One possibility is that it reflects a reduced side bias tendency in the lesioned rats. This possibility is suggested by our earlier finding that the duration of the chance phase in reversal learning tasks is significantly and inversely related to the extent to which subjects exhibit a side bias during learning of these tasks (Garavan, Morgan, Mactutus, et al., 2000). However, no treatment differences in side bias were observed (analyses not included). In sum, further studies are needed to determine both the cognitive and the neural bases of the shortened chance phase found in the current study.

Although we found significant associative impairment in the L40 rats in both tasks, it should be noted that the deficit was moderate. All rats in this group successfully acquired the tasks, albeit at a slower rate. It is, therefore, very possible that some recovery of function may have occurred in the L40 group as well as the L10 group. As mentioned, although peak synaptogenesis has been completed by PND40 for most neural structures thought to be involved in reversal learning, our rats sustained lesions in adolescence at the outer limit of this window. Thus, the L40 group may show recovery of function that would not be observed by subjects lesioned later in adulthood. Moreover, neuroimaging studies showed that substantial reorganization of function occurs in the weeks after injury in adults, usually accompanied by at least a partial recovery of behavioral function (Weiller, 1998; Weiller, Ramsay, Wise, Friston, & Frackowiak, 1993). Higher resolution electrophysiological studies of nonhuman adult animals also showed that, within seconds of nervous system damage, major functional reorganization begins (Krupa et al., 1999; Nicolelis et al., 1993). Additional future experiments should include a treatment group with lesions made much later in life to explore possible differential recovery of function after lesions made in adolescence versus adulthood.

In contrast to any minor recovery shown by the L40 rats, L10 rats did not differ from CTR rats in overall learning rate and showed no associative impairment in the in-depth analyses. Their apparently normal performance in the associative phase may have stemmed from major morphological plasticity in addition to functional plasticity. Studies by Kolb et al. (reviewed in Kolb, 1995) revealed that rats that sustain major cortical damage at about PND10 show dendritic sprouting and presumably increased synapse formation throughout the cortex of the damaged hemisphere. In contrast, rats lesioned before dendritic and axonal sprouting and synapse formation as well as rats lesioned after that time show neither as much behavioral recovery nor the same extent of morphological change in response to the lesion. Our results demonstrate that rats sustaining lesions to the amygdala, a subcortical structure, on PND10 fully recover their associative function, whereas rats lesioned after major synaptogenesis do not. It remains to be determined where the putative morphological changes occurred. Likely sites are structures known to play a role in associative learning, such as the orbitofrontal cortex (Ragozzino et al., 1999), the dorsal striatum (Kolb, 1977), and the mediodorsal thalamus (McBride & Slotnick, 1997).

Prior Studies of Amygdala Lesions and Associative Ability

Our results confirm previous reports that adult amygdala lesions significantly impair reversal learning. Similar deficits in object reversal learning have been observed in adult monkeys with combined hippocampal and amygdala lesions (Pribram et al., 1969; Spevack & Pribram, 1973) and amygdala lesions alone (Aggleton & Passingham, 1981; Douglas & Pribram, 1966; Jones & Mishkin, 1972; Schwartzbaum & Poulos, 1965). In studies of amygdala-lesioned rodents, Kentridge et al. (1991) and Eleftheriou et al. (1972) also found significant learning impairments on tests of object reversal and spatial reversal, respectively. Notably, the latter study only found significant lesion effects on learning when the damage included the cortical or basolateral nuclei. The combination of these studies with the present results suggests that amyg-

dala damage in adult animals can impair reversal learning across multiple modalities. Moreover, our in-depth analyses revealed that the impairment in the L40 group was specific to the postchance learning phases of the tasks. These findings are consistent with other studies reporting a deficit in postperseverative learning after amygdala lesions in primates (Aggleton & Passingham, 1981; Douglas & Pribram, 1966; Jones & Mishkin, 1972; Pribram et al., 1969; Spevack & Pribram, 1973), although another study found that lesioned rats were equally impaired across all phases (Kentridge et al., 1991).

The lack of an associative impairment in the L10 group supports Molino's (1975) findings using a conditioned avoidance task. However, our results concerning delayed alternation and position discrimination reversal learning contrast with those of Thompson (1981). One explanation that can account for the results of these two studies as well as the present findings is that significant recovery of function is most likely to occur when the amygdala damage occurs at the time of peak synaptogenesis. Emerging data provide an explanation for this putative phenomenon: Lesions sustained at this time have the capacity to induce robust axonal plasticity in distal sites and alter the developmental timing in those sites, resulting in a prolonged plastic state, which may support recovery of function by those areas (Butler, Uryu, Morehouse, Rougon, & Chesselet, 1997). Such research supports the findings that the exact timing of the lesion relative to events in neural development may be critical to the outcome and provides an explanation for this observed pattern.

It should be noted, however, that this factor is likely not the only one that determines the degree of recovery of function after early brain injury. For example, the characteristics of the task and the exact brain circuits on which it depends appear to also be critical determinants. Molino (1975) tested subjects on a conditioned emotional response task that assessed the disruption of feeding behavior in response to a tone that predicted an electrical shock. Contrary to the results for the conditioned avoidance task also administered in that study, the conditioned disruption of feeding did not reveal recovery of function for rats lesioned at PND10 relative to those lesioned at PND60. The disparate results obtained in these tasks may relate to the extent to which the behavioral measures in each task reflect the functioning of the central nucleus versus the basolateral nucleus. The measure used in the conditioned emotional response task (disruption of feeding) has been shown to depend heavily on the central nucleus in addition to the basolateral nucleus, whereas the conditioned avoidance response more specifically reflects the functioning of the basolateral nucleus (e.g., LeDoux, Iwata, Cicchetti, & Reis, 1988). Broadly consistent with the findings and ideas of Weiller (1998), it is possible that the anatomy of the central nucleus and its outputs is less redundant than that of the basolateral nucleus complex, allowing less capacity for recovery after damage irrespective of the time at which it occurs. In support of this distinction, Maren (1999) demonstrated that extensive overtraining mitigated the deficits in conditional freezing resulting from lesion of the basolateral nucleus, suggesting that redundant neural circuitry for this type of learning may exist.

Caveats

Two caveats to the conclusions from the present study should be noted. First, it is possible that damage to several collateral structures could have contributed to the observed behavioral effects. Most rats sustained partial damage to the caudate nucleus, the stria terminalis, and portions of the hippocampus. Smaller subsets of rats sustained damage to the globus pallidus and the basal forebrain. We were unable to analyze the separate contributions of damage to these structures, because such damage was not sufficiently independent. However, previous studies demonstrated that damage to the caudate (Kolb, 1977) and possibly also to the hippocampus (e.g., Whishaw & Tomie, 1997) leads to perseveration during reversal learning, which was not seen in our rats. Thus, it seems unlikely that the observed behavioral impairment was due to the collateral damage sustained.

A second caveat pertains to the use of electrolytic lesions. As discussed, the need to include a very early lesion in this study (PND10) precluded the use of excitotoxic lesions, which spare extrinsic fibers of passage. Thus, we cannot rule out the possibility that the dysfunction seen in the L40 group may reflect at least in part damage to fibers of passage in addition to, or instead of, amygdala neurons. Nevertheless, multiple studies using excitotoxic lesions affirm the role of the amygdala, specifically the basolateral and lateral nuclei, in linking cues and affective significance (Cador et al., 1989; Everitt et al., 1991; Hiroi & White, 1991; Maren, Aharonov, & Fanselow, 1996), although some studies and reviews suggested that these nuclei play a more subtle role than previously envisioned (e.g., Burns, Everitt, & Robbins, 1999; Cahill & McGaugh, 1998).

Summary and Conclusions

We explored the effect of early amygdala lesions in comparison to similar lesions made later in development. On an olfactory serial reversal task, it was revealed that lesions at PND40 significantly but subtly impair reversal learning. However, similar lesions at PND10 produced no associative deficit, suggesting that significant sparing or recovery of function occurred. However, it should be noted that the lack of associative impairment of the L10 rats does not imply that these rats were normal, as indicated by the shortened chance phase they exhibited. It is also possible that these rats would be impaired on other tests of amygdala function. Nevertheless, this study shows that the brain is capable of recovering or reorganizing to ameliorate damage to amygdala circuits subserving associative learning if the damage is sustained during early development.

References

Aggleton, J. P., & Passingham, R. E. (1981). Syndrome produced by lesions of the amygdala in monkeys (*Macaca mulatta*). *Journal of Comparative and Physiological Psychology, 95,* 961–977.

Aisaka, A., Aimi, Y., Yasuhara, O., Tooyama, I., Kimura, H., & Shimada, M. (1999). Two modes of corticospinal reinnervation occur close to spinal targets following unilateral lesion of the motor cortex in neonatal hamsters. *Neuroscience, 90,* 53–67.

Burns, L. H., Everitt, B. J., & Robbins, T. W. (1999). Effects of excitotoxic lesions of the basolateral amygdala on conditional discrimination learning with primary and conditioned reinforcement. *Behavioural Brain Research, 100,* 123–133.

Butler, A. K., Uryu, K., Morehouse, V., Rougon, G., & Chesselet, M. F. (1997). Regulation of the polysialylated form of the neural cell adhesion molecule in the developing striatum: Effects of cortical lesions. *Journal of Comparative Neurology, 389,* 289–308.

Cador, M., Robbins, T. W., & Everitt, B. J. (1989). Involvement of the amygdala in stimulus-reward associations: Interaction with the ventral striatum. *Neuroscience, 30,* 77–86.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neuroscience, 21,* 294–299.

Cinaz, P., Guvenir, T., & Gonlusen, G. (1993). Lipoid proteinosis: Urbach-Wiethe disease. *Acta Paediatrica, 82,* 892–893.

Darian-Smith, C., & Gilbert, C. D. (1994). Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature, 368,* 737–740.

Dicks, D., Myers, R. E., & Kling, A. (1969). Uncus and amygdala lesions: Effects on social behavior in the free-ranging rhesus monkey. *Science, 165,* 69–71.

Douglas, R. J., & Pribram, K. H. (1966). Learning and limbic lesions. *Neuropsychologia, 4,* 197–220.

Eleftheriou, B. E., Elias, M. F., & Norman, R. L. (1972). Effects of amygdaloid lesions on reversal learning in the deermouse. *Physiology and Behavior, 9,* 69–73.

Evenden, J. L., Marston, H. M., Jones, G. H., Giardini, V., Lenard, L., Everitt, B. J., & Robbins, T. W. (1989). Effects of excitotoxic lesions of the substantia innominata, ventral and dorsal globus pallidus on visual discrimination acquisition, performance and reversal in the rat. *Behavioural Brain Research, 32,* 129–149.

Everitt, B. J., Cador, M., & Robbins, T. W. (1989). Interactions between the amygdala and ventral striatum in stimulus-reward associations: Studies using a second-order schedule of sexual reinforcement. *Neuroscience, 30,* 63–75.

Everitt, B. J., Morris, K. A., O'Brien, A., & Robbins, T. W. (1991). The basolateral amygdala-ventral striatal system and conditioned place preference: Further evidence of limbic-striatal interactions underlying reward-related processes. *Neuroscience, 42,* 1–18.

Gaffan, D. (1992). Amygdala and the memory of reward. In J. P. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory and mental dysfunction* (pp. 471–483). New York: Wiley-Liss.

Gaffan, D., & Harrison, S. (1987). Amygdalectomy and disconnection in visual learning for auditory secondary reinforcement by monkeys. *Journal of Neuroscience, 7,* 2285–2292.

Garavan, H., Morgan, R. E., Hermer-Vazquez, L., Levitsky, D. A., & Strupp, B. J. (2000). Enduring effects of early lead exposure: Evidence for a specific deficit in associative ability. *Neurotoxicology and Techtology, 22,* 151–164.

Garavan, H., Morgan, R. E., Mactutus, C. F., Levitsky, D. A., Booze, R. M., & Strupp, B. J. (2000). Impaired selective attention in rats exposed to cocaine prenatally: Evidence from extradimensional shift and serial reversal tasks. *Behavioral Neuroscience, 114,* 725–738.

Garraghty, P. E., & Kaas, J. H. (1992). Dynamic features of sensory and motor maps. *Current Opinion in Neurobiology, 2,* 522–527.

Gilbert, C. D. (1998). Adult cortical dynamics. *Physiological Review, 78,* 467–485.

Granger, B., Tekaia, F., Le Sourd, A. M., Rakic, P., & Bourgeois, J. P. (1995). Tempo of neurogenesis and synaptogenesis in the primate cingulate mesocortex: Comparison with the neocortex. *Journal of Comparative Neurology, 360,* 363–376.

Hart, T., Chaimas, N., Moore, R. Y., & Stein, D. G. (1978). Effects of nerve growth factor on behavioral recovery following caudate nucleus lesions in rats. *Brain Research Bulletin, 3,* 245–250.

Hatfield, T., Han, J. S., Conley, M., Gallagher, M., & Holland, P. (1996). Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects. *Journal of Neuroscience, 16,* 5256–5265.

Hilson, J., & Strupp, B. J. (1997). Analyses of response patterns clarify lead effects in olfactory reversal and extra-dimensional shift tasks: Assessment of inhibitory control, associative ability, and memory. *Behavioral Neuroscience, 111,* 532–542.

Hiroi, N., & White, N. M. (1991). The lateral nucleus of the amygdala mediates expression of the amphetamine-produced conditioned place preference. *Journal of Neuroscience, 11,* 2107–2116.

Hoon, A. H., Jr., & Reiss, A. L. (1992). The mesial-temporal lobe and autism: Case report and review. *Developmental Medicine and Child Neurology, 34,* 252–259.

Jacobsen, L. K., Giedd, J. N., Vaituzis, A. C., Hamburger, S. D., Rajapakse, J. C., Frazier, J. A., Kaysen, D., Lenane, M. C., McKenna, K., Gordon, C. T., & Rappoport, J. L. (1996). Temporal lobe morphology in childhood-onset schizophrenia. *American Journal of Psychiatry, 153,* 355–361.

Jones, B., & Mishkin, M. (1972). Limbic lesions and the problem of stimulus-reinforcement associations. *Experimental Neurology, 36,* 362–377.

Kaas, J. H. (1999). Is most of neural plasticity in the thalamus cortical? *Proceedings of the National Academy of Sciences, USA, 96,* 7622–7623.

Kentridge, R. W., Shaw, C., & Aggleton, J. P. (1991). Amygdaloid lesions and stimulus-reward associations in the rat. *Behavioural Brain Research, 42,* 57–66.

Kolb, B. (1977). Studies on the caudate-putamen and the dorsomedial thalamic nucleus of the rat: Implications for mammalian frontal lobe functions. *Physiology & Behavior, 18,* 237–244.

Kolb, B. (1987). Recovery from early cortical damage in rats: I. Differential behavioral and anatomical effects of frontal lesions at different ages of neural maturation. *Behavioral Brain Research, 25,* 205–220.

Kolb, B. (1990). Sparing and recovery of function. In B. Kolb & R. C. Tees (Eds.), *The cerebral cortex of the rat* (pp. 537–561). Cambridge, MA: MIT Press.

Kolb, B. (1995). *Brain plasticity and behavior.* Mahwah, NJ: Erlbaum.

Kolb, B., & Gibb, R. (1991). Sparing of function after neonatal frontal lesions correlates with increased dendritic branching: A possible mechanism for the Kennard effect. *Behavioral Brain Research, 43,* 51–56.

Kolb, B., & Gibb, R. (1993). Possible anatomical basis of recovery of spatial learning after neonatal frontal lesions in rats. *Behavioral Neuroscience, 107,* 799–811.

Kolb, B., Gibb, R., Gorny, G., & Whishaw, I. Q. (1998). Possible regeneration of rat medial frontal cortex following neonatal frontal lesions. *Behavioural Brain Research, 91,* 127–141.

Kolb, B., Holmes, C., & Whishaw, I. Q. (1987). Recovery from early cortical lesions in rats: III. Neonatal removal of posterior parietal cortex has greater behavioral and anatomical effects than similar removals in adulthood. *Behavioural Brain Research, 26,* 119–137.

Kolb, B., Petrie, B., & Cioe, J. (1996). Recovery from early cortical damage in rats: VII. Comparison of the behavioural and anatomical effects of medial prefrontal lesions at different ages of neural maturation. *Behavioural Brain Research, 79,* 1–13.

Kolb, B., & Sutherland, R. J. (1992). Noradrenaline depletion blocks behavioral sparing and alters cortical morphogenesis after neonatal frontal cortex damage in rats. *Journal of Neuroscience, 12,* 2221–2230.

Kolb, B., Sutherland, R. J., & Wishaw, I. Q. (1983). Neonatal hemidecortication or frontal cortex ablation produces similar behavioral sparing but opposite effects on morphogenesis of remaining cortex. *Behavioral Neuroscience, 97,* 154–158.

Kolb, B., & Whishaw, I. Q. (1985). Earlier is not always better: Behavioral dysfunction and abnormal cerebral morphogenesis following neonatal lesions in the rat. *Behavioral Brain Research, 17,* 25–43.

Krupa, D. J., Ghazanfar, A. A., & Nicolelis, M. A. (1999). Immediate thalamic sensory plasticity depends on corticothalamic feedback. *Proceedings of the National Academy of Sciences, 96,* 8200–8205.

LeDoux, J. E. (1995). In search of an emotional system in the brain: Leaping from fear to emotion and consciousness. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 1049–1061). Cambridge, MA: MIT Press.

LeDoux, J. E., Iwata, J., Cicchetti, P., & Reis, D. J. (1988). Different

projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *Journal of Neuroscience, 8,* 2517–2529.

Maren, S. (1999). Neurotoxic basolateral amygdala lesions impair learning and memory but not the performance of conditional fear in rats. *Journal of Neuroscience, 19,* 8696–8703.

Maren, S., Aharonov, G., & Fanselow, M. S. (1996). Retrograde abolition of conditional fear after excitotoxic lesions in the basolateral amygdala of rats: Absence of a temporal gradient. *Behavioral Neuroscience, 110,* 718–726.

Markus, E. J., & Petit, T. L. (1987). Neocortical synaptogenesis, aging, and behavior: Lifespan development in the motor-sensory system of the rat. *Experimental Neurology, 96,* 262–278.

McBride, S. A., & Slotnick, B. (1997). The olfactory thalamocortical system and odor reversal learning examined using an asymmetrical lesion paradigm in rats. *Behavioral Neuroscience, 111,* 1273–1284.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory systems: Hippocampus, amygdala, and dorsal striatum. *Behavioral Neuroscience, 107,* 3–22.

Mitchell, J. A., Channell, S., & Hall, G. (1985). Response-reinforcer associations after caudate-putamen lesions in the rat: Spatial discrimination and overshadowing-potentiation effects in instrumental learning. *Behavioral Neuroscience, 99,* 1074–1088.

Molino, A. (1975). Sparing of function after infant lesions of selected limbic structures in the rat. *Journal of Comparative and Physiological Psychology, 89,* 868–881.

Nicolelis, M. A., Lin, R. C., Woodward, D. J., & Chapin, J. K. (1993). Induction of immediate spatiotemporal changes in thalamic networks by peripheral block of ascending cutaneous information. *Nature, 361,* 533–536.

Nowell, M. A., Hackney, D. B., Muraki, A. S., & Coleman, M. (1990). Varied MR appearance of autism: Fifty-three pediatric patients having the full autistic syndrome. *Magnetic Resonance Imaging, 8,* 811–816.

Paxinos, G., & Watson, C. (1986). *The rat brain in stereotaxic coordinates* (2nd ed.). New York: Academic Press.

Pitkanen, A., Tuunanen, J., Kalviainen, R., Partanen, K., & Salmenpera, T. (1998). Amygdala damage in experimental and human temporal lobe epilepsy. *Epilepsy Research, 32,* 233–253.

Pribram, K. H., Douglas, R. J., & Pribram, B. J. (1969). The nature of nonlimbic learning. *Journal of Comparative and Physiological Psychology, 69,* 765–772.

Pons, T. P., Garraghty, P. E., Ommaya, A. K., Kaas, J. H., Taub, E., & Mishkin, M. (1991). Massive cortical reorganization after sensory deafferentation in adult macaques. *Science, 252,* 1857–1860.

Ragozzino, M. E., Detrick, S., & Kesner, R. P. (1999). Involvement of the prelimbic-infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. *Journal of Neuroscience, 19,* 4585–4594.

Sabel, B. A., Kardon, G. B., & Stein, D. G. (1983). Behavioral effects of intracerebral injections of renin and captopril in intact and brain-damaged rats. *Brain Research Bulletin, 11,* 637–642.

Sananes, C. B., & Campbell, B. A. (1989). Role of the central nucleus of the amygdala in olfactory heart rate conditioning. *Behavioral Neuroscience, 103,* 519–525.

Sarter, M., & Markowitsch, H. J. (1985). Involvement of the amygdala in learning and memory: A critical review, with emphasis on anatomical relations. *Behavioral Neuroscience, 99,* 342–380.

SAS Institute. (1990). PROC MIXED (Version 6.09) [Computer software]. Cary, NC: Author.

Schuckman, H., Kling, A., & Orbach, J. (1969). Olfactory discrimination in monkeys with lesions in the amygdala. *Journal of Comparative and Physiological Psychology, 67,* 212–215.

Schwartzbaum, J. S., & Poulos, D. A. (1965). Discrimination behavior after amygdalectomy in monkeys. *Journal of Comparative and Physiological Psychology, 60,* 320–328.

Seitz, R. J., Hoflich, P., Binkofski, F., Tellman, L., Herzog, H., & Freund, H.-J. (1998). Role of the premotor cortex in recovery from middle cerebral artery infarction. *Archives of Neurology, 55,* 1081–1087.

Snedecor, G. W., & Cochran, W. G. (1989). *Statistical methods* (8th ed.). Ames: Iowa State University Press.

Spevack, A. A., & Pribram, K. H. (1973). Decisional analysis of the effects of limbic lesions on learning in monkeys. *Journal of Comparative and Physiological Psychology, 82,* 211–226.

Spiegler, B. J., & Mishkin, M. (1981). Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. *Behavioural Brain Research, 3,* 303–317.

Sullivan, R. M., & Wilson, D. A. (1993). Role of the amygdala complex in early olfactory associative learning. *Behavioral Neuroscience, 107,* 254–263.

Swanson, L. W., & Petrovich, G. D. (1998). What is the amygdala? *Trends in Neuroscience, 21,* 323–331.

Taghzouti, K., Louilot, A., Herman, J. P., Le Moal, M., & Simon, H. (1985). Alternation behavior, spatial discrimination, and reversal disturbances following 6-hydroxydopamine lesions in the nucleus accumbens of the rat. *Behavioral and Neural Biology, 44,* 354–363.

Thompson, C. I. (1981). Learning in rhesus monkeys after amygdalectomy in infancy or adulthood. *Behavioural Brain Research, 2,* 81–101.

Uryu, K., Butler, A. K., & Chesselet, M. F. (1999). Synaptogenesis and ultrastructural localization of the polysialylated neural cell adhesion molecule in the developing striatum. *Journal of Comparative Neurology, 405,* 216–232.

Weiller, C. (1998). Imaging recovery from stroke. *Experimental Brain Research, 123,* 13–17.

Weiller, C., Ramsay, S. C., Wise, R. J. S., Friston, K. J., & Frackowiak, R. S. J. (1993). Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. *Annals of Neurology, 33,* 181–189.

Whishaw, I. Q., & Tomie, J. A. (1997). Perseveration on place reversals in spatial swimming pool tasks: Further evidence for place learning in hippocampal rats. *Hippocampus, 7,* 361–370.

Xerri, C., Coq, J. O., Merzenich, M. M., & Jenkins, W. M. (1996). Experience-induced plasticity of cutaneous maps in the primary somatosensory cortex of adult monkeys and rats. *Journal of Physiology Paris, 90,* 277–287.

Yeo, R. A., Hodde-Vargas, J., Hendren, R. L., Vargas, L. A., Brooks, W. M., Ford, C. C., Gangestad, S. W., & Hart, B. L. (1997). Brain abnormalities in schizophrenia-spectrum children: Implications for a neurodevelopmental perspective. *Psychiatry Research, 76,* 1–13.

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