

Research Report

Recovery of function after neonatal ablation of the auditory cortex in rats (*Rattus norvegicus*)

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Abstract

Functional recovery following neonatal ablation of the auditory cortex was surveyed in 28 rats. Fourteen neonatal-lesioned rats had their temporal cortex lesioned on the date of birth (P1); 7 adult-lesioned rats had their auditory cortex lesioned at P60; and 7 rats served as controls. The training consisted of two phases using tasks with a Go/No Go procedure. The first task was to detect the presentation of a tone pulse. The second task was to discriminate the pulse rate of a tone pulse. Results showed that the achievements of neonatal-lesioned and control groups were comparable in both tasks. Adult-lesioned rats, however, failed to discriminate temporal patterns, although they could detect tone presentation as efficiently as the other two groups. These findings suggested that discrimination of temporal patterns could be a critical function of the auditory cortex and that brain injury in infancy was more compensated than the comparable damage in adulthood. Neurological plasticity was suggested in the recovery of function in our neonatal-lesioned animals.

Keywords: Auditory cortex; Auditory discrimination; Developmental plasticity; Neonatal lesion; Rat; Recovery of function

1. Introduction

1.1. Recovery from early brain damage

Early brain damage has both behavioral and neuroanatomical consequences which differ from the effects of lesions in the adult. Recovery of function after a brain lesion is more extensive for the early lesion. In the present research, auditory discrimination after the lesion of the auditory cortex in neonatal rats was studied with the purpose of testing the 'Kennard Principle'. According to this principle, there is greater recovery from brain damage sustained neonatally as compared to a similar lesion received in adulthood.

1.2. Auditory cortical areas

Auditory cortex of adult rats fundamentally consists of topographically organized primary auditory cortex (Te1) and topographically less organized secondary

auditory cortex (Te2 and Te3). Te1 is innervated mainly from the ventral division of the medial geniculate nucleus which provides a precise representation of the acoustic signal [13]. On the other hand, Te2 and Te3 are innervated mainly from the dorsal division of the medial geniculate nucleus which provides information less tightly coupled to the physical components of sound [12].

Additionally, areas around the secondary somatosensory (Par2) and the secondary visual (Oc2L) areas are included in the auditory cortex. When click and vibrissal stimulation were introduced simultaneously, an area uniquely responding to combined stimulus or a polysensory zone, was detected between the primary somatosensory areas (Par1) and Te1, partially overlapping Par2 [10]. Similarly, simultaneous presentation of click and flash stimuli revealed that there are polysensory zones from the junction of the primary visual areas (Oc1) and Oc2L to the junction of Te1 and Te2 [3].

1.3. Behavioral studies of the auditory cortex

Tasks, such as intensity discrimination [41,62] and frequency discrimination [4,8,14,19,25,29,30,38,41,72,

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73] and detection of the onset of a tone [33], are not impaired after cortical ablation.

Ablation of the auditory cortex in most mammalian species results in severe deficits in sound localization. In the cat, bilateral ablation of the auditory cortex results in a complete inability to localize brief sounds [24,47,48,68]. Dogs, monkeys and ferrets also suffer impairments in sound localization following bilateral ablation of the auditory cortex [22,23,27,28,74].

In contrast, studies with the rat, hedgehogs and bush-babies reveal little impairment in sound localization following bilateral ablation of the auditory cortex [55]. In a multiple-choice apparatus, normal rats localize a single click at poor performance levels [26]. Thus, normal rats have considerable difficulty in localizing sounds that depend most on the primary auditory cortex in the cat and ferret. Behavioral studies indicated that the rat's auditory cortex is not essential for the localization of sound in space. While bilateral destruction of the medial geniculate body also fails to produce an incapacity for sound localization, even in a two-choice situation, severe deficits are suggested only if the inferior colliculus and the neighboring lateral tegmentum are damaged [32].

Also, bilateral lesion of the auditory cortex in the rat produces no obvious change in conditioned autonomic response or conditioned emotional responses to auditory stimuli. On the other hand, bilateral lesions of the medial geniculate nucleus decreased the conditioned emotional and autonomic responses to sound [35,36]. Fear conditioning depends on the transmission of auditory conditioned stimulus information to the lateral amygdala through either thalamo-amygdala or thalamo-cortico-amygdala pathways [61]. Therefore, the auditory cortex is not essential for conditioned emotional response to sounds.

1.4. Critical function of the auditory cortex

At any given level of the auditory system, tones of different frequencies excite different nerve fibers. The greater the intensity of a tone, the more fibers the tone excites. Intensity and frequency can be processed even in the cochlea nucleus [15]. Thus, subcortical structures can provide information about frequency, intensity and direction of each stimulus component.

Recognition of sound patterns was impaired following bilateral auditory cortices in cats [6,7,11,16,30,64] and in monkey [25]. Moreover, auditory cortical neurons in the cat can exhibit unique responses to a tone presented in a sequence than to the same tone presented alone. Neurons in the auditory cortex encoded changes of tone sequences as discharge patterns which are not simply a summation of the responses to the individual tones [40]. Such *gestalt* pattern recognition should be one of the critical functions of the auditory cortex.

It is important to note that 'temporal pattern' refers to a temporal constellation of pulses. Temporal pattern is not assessed at the subcortical level. Temporal pattern may be associated with phase locking in the auditory fibers. However, these fibers lock to pitch information, but never preserve the temporal feature of sound. For instance, when a 1-kHz pure-tone burst was presented, auditory nerves were activated at a 1-ms interval. But auditory fibers constantly fire at 1-ms intervals regardless of whether the pure-tone burst is repeated at a 100- or 1000-ms interval. Therefore, the phase-locked information merely reflects spectral features of the stimuli, but never preserves the auditory pulse rate.

The purpose of the present experiment was to study whether functional recovery after the neonatal lesion of the auditory cortex could be shown with rats using operant techniques with auditory temporal discrimination.

2. Materials and methods

2.1. Subjects

The subjects were 28 Wistar rats (*Rattus norvegicus*) born in our laboratory. They were divided into 3 groups: 7 male controls; 14 neonatal-lesioned rats of both sexes; and 7 male adult-lesioned rats. Lesioned pups were brought up with their mother until weaning. Matured rats were housed individually in hanging wire-mesh cages in a temperature- and humidity-controlled vivarium maintained on a 12–12 h dark–light cycle.

2.2. Auditory cortical lesion

2.2.1. Neonatal lesion of the auditory cortex

Neonatal lesions were performed on the day of birth (P1). These pups were anesthetized by hypothermia. The scalp was sagittally incised. The skull and dura overlying the temporal cortex were incised and reflected, and then, the temporal cortex was bilaterally aspirated with a suction pipette. The location of the target was identified according to the characteristic pattern of the cerebral vasculature and the atlas of the developing rat brain [51]. After completion of surgery, a gelatin sponge was fitted into the cortical defect and antibiotics were given. The incised skin was sutured and lesioned pups were allowed to recover in hot water (ca. 37°C). All the processes of neonatal-lesion were conducted within 12 h of birth. In the neonatal-lesion, the bilateral temporal cortex was lesioned simultaneously. When the lesioned pups were 9 weeks old, the behavioral training was started.

2.2.2. Adult lesion of the auditory cortex

Adult lesions were performed at P60. Surgery was conducted under anesthesia with ketamine (6 mg/kg, i.m.) and xylazine (0.6 mg/kg, i.m.). The animal was placed in a stereotaxic apparatus for stability. The scalp was incised and temporal muscle was detached. Xylocaine was injected around the area of incision. Then, a craniotomy was performed over the target cortex and the bone flap was kept in saline. Afterwards, the auditory cortex was aspirated with a suction pipette. The location of the auditory cortex was determined based on the stereotaxic atlas [50]. When the ablation was completed, a gelatin sponge was placed in the cortical defect. The stored piece of bone was replaced and skin incision was repaired, and antibiotic treatment was given. Adult-lesions were conducted sequentially: one side was lesioned first and the other side was lesioned followed by a recovery period of 3 weeks. Behavioral training began 60 days following the second lesion. Thus, the recovery period in both neonatal-lesioned and adult-lesioned rats was the same.

2.3. Behavioral testing

2.3.1. General procedure

Behavioral training consisted of two phases and both were conducted with a Go/No Go procedure. Positive stimuli required a response, and negative stimuli did not. In phase 1, the task was to discriminate whether there was a tone or not. This task was conducted so that rats without temporal cortex could detect the onset of tone stimuli and could acquire stimulus control with the tone stimuli. This task also served as preliminary training for the next phase. After the completion of phase 1, phase 2 started. In this phase, the task was to discriminate the temporal patterns of the stimuli. Each animal was therefore tested on two discrimination tasks (phase 1 and phase 2).

The two trainings allowed a comparison of the learning ability of individual animals between groups without considering the variance due to animal differences by using ratio score. The ratio score was calculated for each animal as the number of sessions needed in discrimination task (phase 2) divided by that in detection task (phase 1).

With such a procedure, whether effect of the lesion on the auditory ability was general or specific can be clarified.

2.3.2. Apparatus

Behavioral training was carried out in the conventional operant chamber with a single lever placed in an acoustically isolated room. A loudspeaker (Yamaha, MS-10) was placed in front of the chamber, through which stimuli were presented. Tone stimuli were generated from a digital sampler (Akai, S-950). The experi-

ments were controlled by a personal computer (Sanyo, PHC-FD70).

2.3.3. Stimuli

A 4-kHz pure tone was recorded from a pure tone generator (Yokokawa Denki, 0V-21A) and was transferred to a digital sampler. This tone was then modified into the experimental stimuli by a commercially available software. The tone stimuli were composed of 4 kHz/50 ms duration pure tone pulses with 10 ms of rising and falling time. The tone bursts were repeatedly presented with a given interval at 70 dB SPL, which is 40 dB above the threshold [31].

The experimental training consisted of two phases. In phase 1, tone pulses were repeatedly presented with 1750-ms intervals for a positive stimulus while no sound was presented for a negative stimulus. In phase 2, the tone pulses were presented with 500- and 3000-ms intervals for positive and negative stimuli, respectively. From previous experiments of temporal discrimination in rats, the mean difference threshold was estimated to be 625 ms in which a 500-ms duration (or interval) was regarded as a standard stimulus, both in a duration [5] and in an interval [69] discrimination. In other words, the typical rat could just barely differentiate a 500-ms duration (or interval) from a 1125-ms duration (or interval). In this case, 625 ms was considered as one unit of just noticeable difference (JND) for time perception. Thus, the task adopted in phase 2 should be easily learned by normal rats since 3000-ms intervals were psychologically separated by 4 JNDs from 500-ms intervals.

2.3.4. Behavioral testing

Each trial lasted for 30 s and stimuli were also presented for 30 s. The sequence of positive and negative trials was determined so that the same stimuli were not presented in 3 or more consecutive trials. In positive trials, responses were rewarded with food on a variable interval 30-s schedule (VI 30 s). Thus, responses were not always followed by food presentation, but only responses emitted on average 30 s after the last food presentation was reinforced. In negative trials, responses were not followed by food presentation. The intertrial interval (ITI) lasted for 6 s, during which no tone was presented and differential reinforcement of other response schedule (DRO) was intermixed. Thus, the ITI was terminated after 6 s if there was no response in this interval, while any response emitted in this period made the ITI longer. When a silent ITI is inserted, animals cannot refer to the stimulus change for which response should be made. Therefore, memory or cognitive ability as well as discrimination ability is involved in selecting the correct response, and the task becomes one of recognition.

Each daily session of both phases consisted of 20

warm-up trials and 50 experimental trials. Data from the warm-up trials were discarded from the analysis. The learning criterion was set at 80% response accuracy on both phases. The response accuracy was calculated as the ratio of the number of responses made in the positive trials against the total number of responses. In both phases, trainings were terminated when the animals attained the criterion in two consecutive sessions. In phase 2, when the criterion was not achieved, training was discontinued at twice as many sessions as taken by the same animal in phase 1. However, at least 40 sessions were conducted in phase 2, since typical control rats could complete the task in the phase 2 by the 40th session.

2.4. Histological procedure

After the learning trainings, animals were anesthetized with an overdose of pentobarbital and perfused through the ascending aorta with a 0.9% NaCl solution followed by 10% formalin. The brain was rinsed overnight in the same fixative and was embedded in 7% agarose. Tissues were cut at 100 μm and stained with Cresyl violet. Stained sections were traced using a projection microscope for reconstruction.

2.5. Data analysis

In order to compare the results of behavioral trainings in each group, the number of sessions needed and the ratio score were compared by Kruskal–Wallis and Mann–Whitney *U*-tests for phases 1 and 2, respectively.

3. Results

3.1. Histology

Fig. 1 contains the serial reconstructions of a representative temporal cortex aspiration in the neonatal (left) and adult rats (right). All the lesions included damage to the Te1 and surrounding area. Typically, in addition to the Te1, the lesion extended caudally to anterior half of the Te2, rostrally to posterior Par2 and dorsally to the lateral posterior Oc2L. There was no direct damage to the thalamus.

Following the auditory cortical lesion, the cochlea nucleus, the trapezoid body and the superior olivary complex were almost normal in both the neonatal- and the adult-lesioned animals. In contrast, neurons in the inferior colliculus and the medial geniculate nucleus were sparse. Cell loss in these structures was more extensive in the neonatal-lesioned animals.

In the neonatal-lesions, the extent of aspirations varied among animals. Large neonatal-lesioned sites extended to the posterior half of Par1. Lesion in the Oc2L was

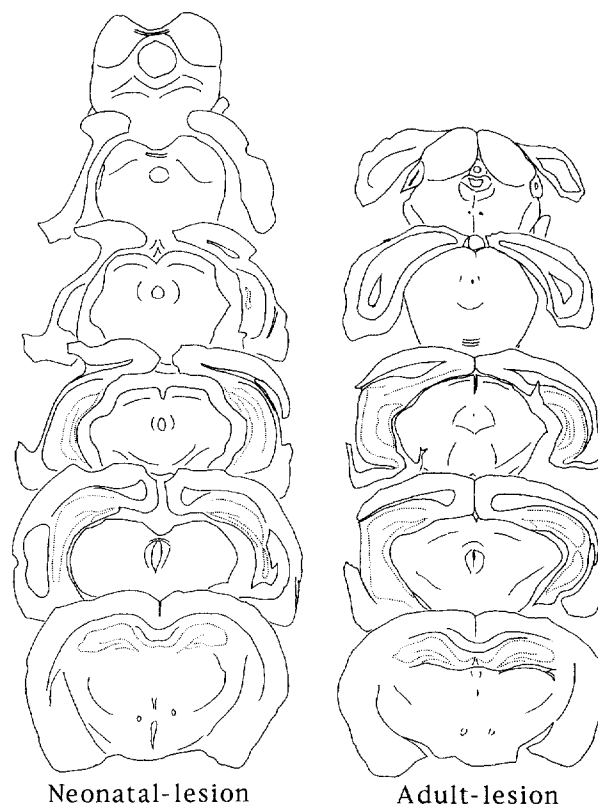


Fig. 1. Representative reconstructions of neonatal (left) and adult lesions (right). Sections were arranged at intervals of 500 μm .

more extensive in the neonatal-lesioned rats. The medial geniculate nucleus in neonatal-lesioned rats had almost disappeared and were displaced posteriorly by about 0.5–1.0 mm compared to normal adult rats. In neonatal-lesions, the hippocampus was occasionally abnormally shaped.

The results of adult aspirations were similar within the group. Adult-lesioned rats appeared to have more restricted damage than neonatal-lesioned animals since the adult-lesions were conducted stereotaxically. In some adult-lesions, part of auditory area was only superficially aspirated. However, such lesions were sufficient to degenerate subcortical auditory structures.

3.2. Behavioral testing

No statistical difference in the number of sessions needed to complete training was found between male and female neonatal-lesioned rats in both phase 1 (Mann–Whitney *U*-test, $Z = 1.097$, $P = 0.2725$) and phase 2 (Mann–Whitney *U*-test, $Z = 0.194$, $P = 0.8465$). Ratio scores also showed that there was no difference in improvement between male and female neonatal-lesioned rats (Mann–Whitney *U*-test, $Z = 0.387$, $P = 0.6985$). Therefore, the data from male- and female-lesioned rats were pooled (Figs. 2–4 and Fig. 5).

Fig. 2 and Fig. 4 show learning curves across sessions

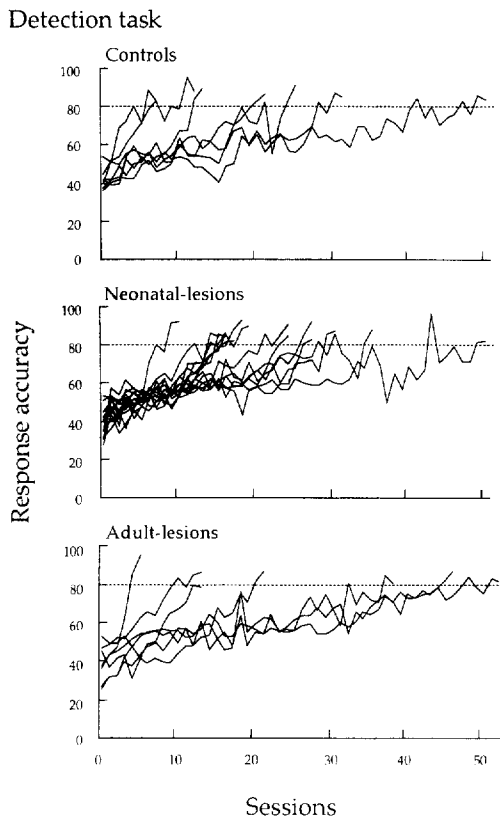


Fig. 2. Learning curves of the rats across sessions in the detection task of phase 1. Top, middle and bottom panels show the results of the control, neonatal-lesion and adult-lesion animals, respectively. Broken lines represent criterion.

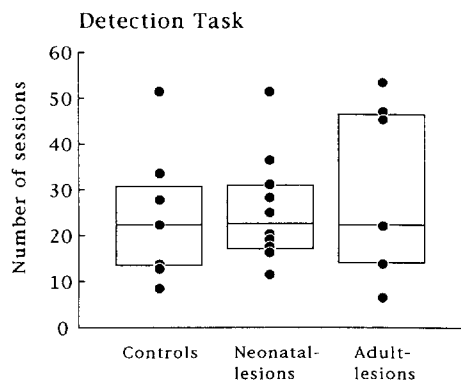


Fig. 3. Box plots of the number of sessions needed to complete the training across groups in the detection task of phase 1. In each box, horizontal lines show the 25th, 50th (median) and 75th percentiles. Left, middle and right distributions represent the results of the control, neonatal-lesion and adult-lesion animals, respectively. Data for individual animals are superimposed on each box.

for each group in phases 1 and 2, respectively. Broken lines represent the criterion of the training. Fig. 3 and Fig. 5 depict the number of sessions needed to complete training for each group in phases 1 and 2, respectively. In these figures, box plots display the 25th, 50th (median) and 75th percentiles of each group. Each filled circle represents the number of session needed in individual

animals for each group. Ratio scores for individual animals in each group are depicted in Fig. 6.

All these figures show that the 3 groups performed similarly on the tone detection task in phase 1. There was no statistically significant difference in the number of sessions needed among the 3 groups (Kruskal–Wallis test, $H=0.254$, $df=2$, $P=0.8807$).

In phase 2, however, adult-lesioned rats could not learn the pattern discrimination task even after twice as long sessions taken in the tone detection task. Contrary to the adult-lesioned rats, the control and neonatal-lesioned rats learned this task similarly. There was no significant difference between neonatal-lesioned rats and the control rats in the number of sessions needed (Mann–Whitney U -test, $Z=1.119$, $P=0.2631$).

These results show that both detection and discrimination achievements in neonatal-lesioned rats and controls were comparable. Moreover, there was no significant difference between neonatal-lesioned rats and controls in the ratio scores (Mann–Whitney U -test, $Z=1.306$, $P=0.1917$). That is, tendencies of the learning in individual animals of both groups were parallel. However, in the neonatal-lesion, the correlation between behavioral results and the tissues were unclear.

4. Discussion

4.1. General conclusion

The aim of the present experiment was to assess auditory discrimination following the removal of auditory cortex in neonatal and adult rats. Two major conclusions can be drawn from this study concerning recovery of behavioral function after ablations of the auditory cortex: (1) auditory discrimination based on a temporal dimension with an operant conditioning paradigm was an appropriate method; and (2) removal of temporal cortex at birth leads to complete recovery of auditory discrimination later. Thus, the Kennard Principle was supported in this research.

It is important to show not only which tasks are affected, but also which tasks are unaffected by lesions. If impairments occur in all learning situations, the lost performance cannot be ascribed to the lesion. The two tests used here showed that ablation of the auditory cortex specifically affected temporal discrimination in adult-lesioned rats and did not affect tone detection. Thus, the detection task conducted in phase 2 involved the characteristic function of auditory cortex. Conversely, it can be concluded that recovery of cortical function had occurred in the neonatal-lesioned rats.

4.2. Validity of behavioral testings

In any discrimination tasks, it is possible that animals refer to a negative stimulus to recognize a positive

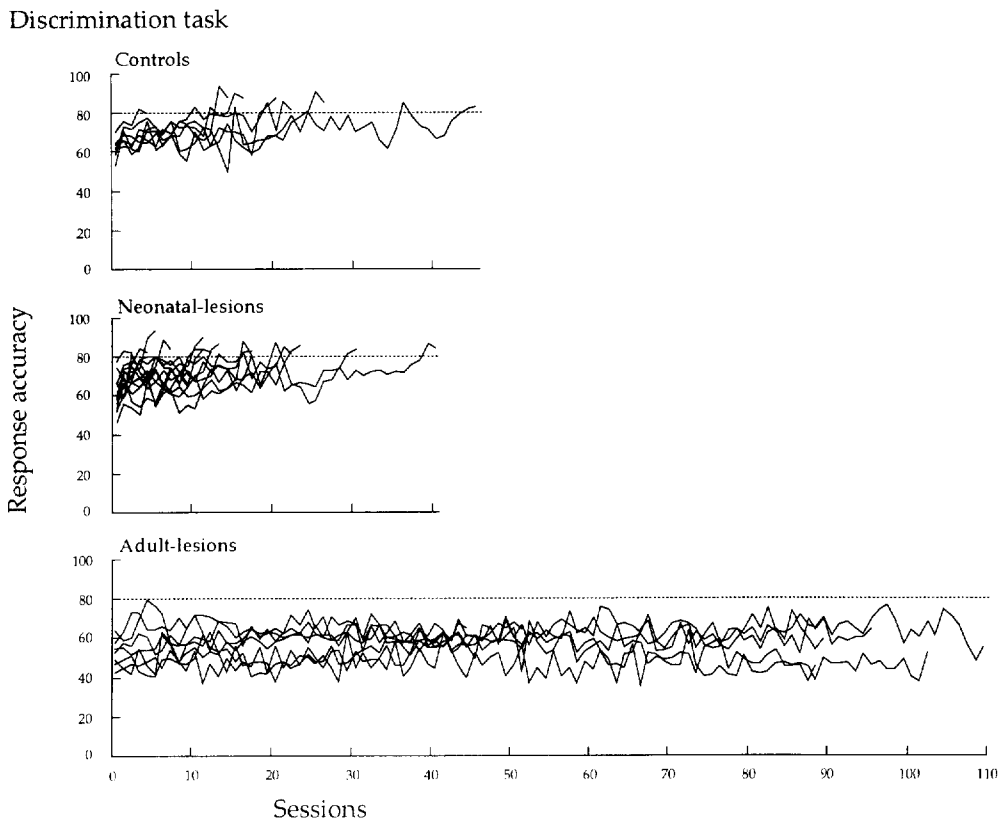


Fig. 4. Learning curves of the rats across sessions in the discrimination task of phase 2. Top, middle and bottom panels show the results of the control, neonatal-lesion and adult-lesion animals, respectively. Broken lines represent criterion. In the case of the adult-lesion, the criterion was not attained after extensive training.

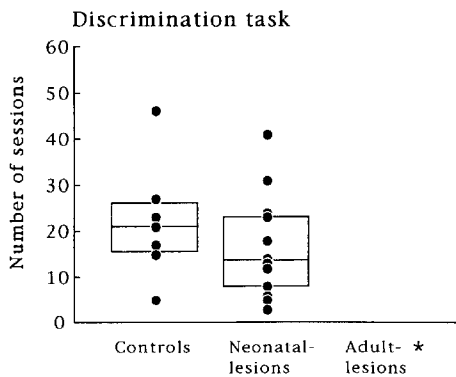


Fig. 5. Box plots of the number of sessions needed to complete the training across groups in the discrimination task of phase 2. In each box, horizontal lines show the 25th, 50th (median) and 75th percentiles. Left and right boxes represent the results of the controls and neonatal-lesions. Data for individual animals are superimposed on each box. *In the case of the adult-lesion, the criterion was not attained after extensive training.

stimulus. In such tasks, animals can make a relative discrimination. By inserting an ITI between trials, however, animals cannot refer to a change in external signals to discriminate stimuli. Thus, animals have to achieve an absolute discrimination. In such a case, discrimination is achieved only if animals establish memory traces or sensory representations. Moreover, the Go/No Go task

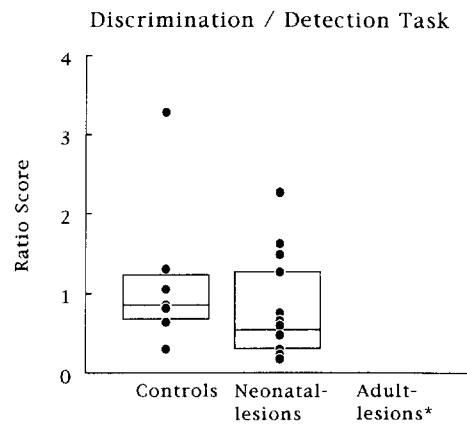


Fig. 6. Box plots of the ratio scores as a result of the battery tests across groups. In each box, horizontal lines show the 25th, 50th (median) and 75th percentiles. This score was calculated as the number of the sessions needed to complete the task in phase 2 by that in phase 1. Left and right boxes represent the results of the controls and neonatal-lesions. Data for individual animals are superimposed on each box. *Same as Fig. 5.

adopted in the present experiment is more sensitive to cognitive deficits than two-alternative procedure [71]. Even in frequency discrimination or localization tasks, long ITIs affect the discrimination ability of lesioned cats [7,41,47]. The task in phase 1 was simple and may

not have required the auditory cortex. On the other hand, it is possible that in phase 2, the rats were required to use the auditory cortex in order to make the discrimination.

4.3. Development of sensory systems

Transient expression of acetylcholinesterase, indicating the beginning of functional axonal connections of the principal sensory thalamus to primary sensory cortical areas, can first be detected at the 4th day of age within the rat's auditory cortex [18,56,57]. Auditory evoked potentials cannot be recorded from the auditory cortex until the 14th day of age [46]. The central nucleus of the inferior colliculus is tonotopically organized in an adult animal. However, in mice, the first low-frequency responses without tonotopy can be recorded from this nucleus at day 10 [60]. The inferior collicular cortex is supposed to mediate audiomotor function (e.g., orienting to a sound source) in adult animals [1,2]. By the 10th day, however, it modulates sensorimotor integration (e.g., tail pinch-induced reflex) which is suggested to shift to the cerebral cortex during the course of cerebral maturation [39]. Simple auditory association occurs by 18 days of age [63]. It has been suggested that fundamental changes in the rat's learning and memory processes occur around the time of weaning [20]. Accordingly, in the present experiment, neonatal-lesions were conducted well before auditory systems were fully functional and animals began auditory associative learning.

4.4. Compensatory recovery of function by other sensory modality

It is improbable that, in our neonatal-lesioned rats, normal subcortical auditory structures, such as medial geniculate nucleus and inferior colliculus were functional since both structures were heavily degenerated. Thus, it is reasonable to assume that normal auditory cortical function, such as temporal discrimination, was attained by structures other than auditory systems.

Anatomically, numerous experiments suggest that sensory projections have little dependence on the target neurons in mature animals, but that these projections are susceptible to the presence of their target in the developing animal [37,42–45,49,52]. In the immature animal, aberrant projections have been produced by unilateral lesion made in the retina, optic chiasma, superior colliculus, visual cortex [17,21,65–67] or auditory cortex [34]. Thus, the developing nervous system flexibly changes its target according to its environment. Therefore, in our neonatal-lesioned rats, reorganization in the brain must have occurred during the course of development.

In the ferret, it has been reported that visual represen-

tation was induced in the auditory cortex following neonatal compound lesions of the unilateral visual cortex, the inferior colliculus and the brachium of the inferior colliculus [58,59,70].

In cats, loss of vision following binocular deprivation from birth was compensated by plastic changes in other modalities. These binocularly deprived cats could localized sound sources more precisely than normal animals [53]. In anterior ectosylvian region, which receives inputs from different sensory modalities, visual deprivation from birth resulted in a crossmodal expansion of the neighboring auditory and somatosensory regions into normally visual territory [54]. In binocularly deprived cats, the ratio of sharply tuned auditory neurons in the anterior ectosylvian region increased and the length of vibrissae was increased. Similarly, barrels were enlarged in neonatally enucleated mice [54]. These findings are interpreted as a form of adaptation of the developing brain to an altered environment.

However, whether the experimentally induced aberrant projections reported so far in the literature contribute to proper functioning is doubtful. When the superior colliculus was damaged soon after birth in neonatal hamsters, optic axons destined for the ablated superior colliculus formed connections with the remaining superior colliculus. However, these connections resulted in maladaptive turning of the head away from food presented in front of the face [67]. In neonatal hamsters, a functional deficit following partial transection of the lateral olfactory tract has also been reported. Mating behavior exhibited in the adult was impaired as a result of collateral sprouts from residual axons that formed aberrant connections [9]. Despite considerable anatomical recovery, the ultimate effect was maladaptive or non-functional behavior.

Recovery of function in our neonatal-lesioned rats must have caused reorganization in the brain. Unlike the animals mentioned above, however, the expected reorganization did not prevent the animals from exhibiting the appropriate responses. Therefore, our neonatally lesioned rat could be a suitable example for the study of recovery after brain lesion. Nevertheless, how the recovery of function from the early brain damage was established in these animals still remains to be clarified.

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