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Long-term retention of learning-induced receptive-field plasticity in the auditory cortex

(frequency tuning/classical conditioning/guinea pig)

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ABSTRACT **Brief learning experience (classical conditioning) induces frequency-specific receptive-field (RF) plasticity in the auditory cortex, characterized as increased response to the frequency of the conditioned stimulus and decreased responses to most other frequencies, including the pretraining best frequency. This experiment asked (*i*) whether learning-induced RF plasticity, established in the waking state, can be expressed under general anesthesia and if so (*ii*) whether it exhibits long-term retention. Pure-tone-frequency RFs were obtained from adult guinea pigs under general anesthesia (sodium pentobarbital or ketamine) before and repeatedly after (1 hr–8 weeks) a 20- to 30-trial session of pairing a non-best-frequency tone with mild footshock. Conditioned-stimulus-specific RF plasticity was expressed under both types of anesthesia and included shifts of the pretraining best frequency toward or even to the frequency of the conditioned stimulus. Moreover, this RF plasticity exhibits long-term retention, being evident 1–8 weeks after training. This satisfies a criterion for the long-term storage of information in the auditory cortex.**

Over the past 40 years, neurophysiological studies of learning have established that Pavlovian (classical) conditioning induces plasticity of neural responses to conditioned stimuli (CSs) in many brain systems. In general, conditioning causes associatively dependent increased responses to the CS, including the sensory neocortex of its modality (for a review of the auditory cortex, see ref. 1). Such plasticity may represent the persistent storage of information, i.e., long-term memory. However, at least two criteria should be satisfied to advance this interpretation. (*i*) The plasticity should be shown to involve a modification of "information" about the CS rather than merely to reflect an increase in neural "excitability." (*ii*) The plasticity should exhibit "long-term retention," that is, endure over weeks or months, periods of time commensurate with behaviorally indexed long-term memory.

We have reported that learning does indeed modify "information" about the CS. Instead of only recording responses to the tonal CS during training, we determined neuronal receptive fields (RFs) for frequency before and after behavioral conditioning. After training, responses to the frequency of the CS were increased, whereas responses to other frequencies, including the pretraining best frequency (BF), were decreased. These opposing changes are sufficient to shift frequency tuning toward or even to the frequency of the CS. In contrast, neurons in sensitization control subjects develop only a general increase in response across their RFs (2–6, 27). Thus associative conditioning produces CS-evoked plasticity in the auditory cortex that represents a modification of "information" about the CS, whereas nonassociative exposure to stimuli produces merely a general increase in "excitability."†

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This study concerns long-term retention. Despite the extensive literature on the neurophysiology of learning, the issue of long-term retention of learning-induced neuronal plasticity seems to have been largely ignored. The purpose of this investigation was to determine the extent to which CS-specific RF plasticity exhibits long-term retention.

MATERIALS AND METHODS

Methods were similar to those reported (4) and only salient differences are described here.

Subjects and Preparation. The subjects were 15 male Hartley guinea pigs (*Cavia porcellus*) obtained from Hilltop Farms, Scottsdale, PA (450–1100 g). While subjects were under general anesthesia [atropine sulfate (0.02 mg/kg)/diazepam (8 mg/kg)/sodium pentobarbital (20 mg/kg) all i.p.], an array of four to eight insulated tungsten microwires (50 μm; impedance, ≈1–3 MΩ at 1 kHz; spaced, 300 μm apart) was implanted into the auditory cortex.‡ After attainment of large-click-evoked potentials on a majority of electrodes in infragranular layers, the array was cemented in place within a pedestal of dental acrylic that contained threaded cylinders for atraumatic fixation of the head during RF determinations.

Recording Sessions and RF Determinations. Unit clusters were recorded from the one or two electrodes per subject that had acceptable waveforms and clear-frequency tuning. Neuronal activity was amplified, filtered (300–3000 Hz), voltage-discriminated, and stored in a brainwave workstation. The spike-level discriminator was kept constant within an electrode for all sessions once set for the pretraining RF determination. The workstation generated a calibrated isointensity ascending frequency series of tone bursts (duration, 100 msec; intertone interval, 400 msec). The discharges to 20 repetitions

Abbreviations: RF, receptive field; CS, conditioned stimulus; BF, best frequency; dB, decibel; SI, shift index; NMDA, *N*-methyl-D-aspartate.

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†It is important to understand that an increase in general excitability due to association is different from an increase in general excitability caused by nonassociative processes, such as sensitization. This distinction has been overlooked. But associative learning could facilitate the processing of a class of stimuli, such as acoustic frequencies, rather than a specific member of the class; specifically, the tonal frequency which is the CS. Although such general learning may be adaptive, "it does not involve a modification of the way in which specific information about the CS itself is represented and stored." In short, to establish that learning specifically alters the processing of information about the CS, it is necessary but not sufficient to demonstrate that the plasticity is due to association.

‡The auditory cortex of the guinea pig has two mirror image tonotopically organized fields aligned in a rostral-caudal direction (7). Recordings were probably obtained from both fields. Responses of neuron clusters themselves were consistent with the characteristics of previous reports from primary auditory cortex in the waking cat and monkey. As the goal of this study was to study long-term retention of RF plasticity from tonotopic auditory fields, the absence of clear attribution of each recording site to either field is not a severe limitation.

of these isointensity frequency series were determined at 10-decibel (dB) intervals, generally from 0 to 80 dB (4).

Experimental Design and Classical Conditioning. To provide a basis for bridging the gap between the neurobiology of learning and memory and sensory neurophysiology, RFs were determined with subjects under general anesthesia, which is the state used in most studies of sensory neurophysiology. After several days of recovery, subjects were deeply anesthetized with either sodium pentobarbital (40 mg/kg) plus diazepam (9 mg/kg) or ketamine (70 mg/kg), xylezine (20 mg/kg), plus diazepam (9 mg/kg). They were placed in a hammock inside an acoustic chamber with temperature maintained by a heating pad. The pedestal was bolted to a rigid post and a calibrated speaker was connected to the ear canal contralateral to the recording sites. After this pretraining RF determination, subjects were allowed to recover in an incubator and returned to the home cage.

Training took place on the next day. Subjects were placed in a Plexiglas wheel with a grid floor, within an acoustic chamber. The auditory stimulus used as the CS was delivered from an overhead speaker with sound levels ≈80 dB throughout the wheel. The frequency of the CS was selected to not be the BF, as determined from the pretraining RF. After 5 min of adaptation, subjects received 20–30 trials of conditioning: CS, 6 sec; unconditioned stimulus (US), 2-sec footshock (1–4 mA) delivered at CS offset. Intertrial intervals averaged 90 sec (range, 60–120 sec). This paradigm reliably produces behavioral conditioning in 5–10 trials (refs. 4 and 8; for review, see ref. 9) and did so in this study. Posttraining RFs were obtained while subjects were under anesthesia, as soon as 1 hr after training but most frequently 24 hr later and at one or more intervals of approximately 1, 2, 4, and 8 weeks after training, as long as satisfactory recordings could be obtained.

Quantification of Neuronal Data. Frequency RFs were calculated by subtracting the average discharge during a pretone period (50 msec) from the average discharge during each tone (10- to 30-msec tuned onset response). The evoked discharge to the 20 presentations of each tone was averaged for each intensity and plotted vs. frequency. Evoked response across frequency at a given stimulus level constitutes the RF. RF difference functions revealed the overall effect of training and were calculated by subtracting the pretraining RF from each posttraining RF of the same intensity. The percent change of response for each intensity at each posttraining retention period was determined for the CS frequency and for the pretraining BF, based on the rate of discharge (spikes per sec) as follows: percent change CS (or BF) = [(rate after CS/rate before CS) × 100] − 100. The relative percent of change for each intensity for each retention period in response to the CS frequency compared to the BF was calculated as CS percent change minus BF percent change.

Criterion for CS-Specific RF Plasticity. The criterion of CS-specific RF plasticity (hereafter called RF plasticity) was based on the change in relative response to the frequency of the CS and the BF. For each intensity within each session, the rate of response (spikes per sec) to the CS was divided by the same measure for the BF. This CS/BF ratio for the pretraining RFs was subtracted from the ratio for the same intensity for each of the posttraining RFs, yielding a ratio difference. An increased response to the CS frequency relative to the BF produces a positive ratio. The criterion of RF plasticity for a retention session was that the ratio difference be at least 0.1 for a majority of stimulus intensities within that session. This ensured that the RF plasticity was consistent across intensity. The criterion ratio difference was selected to be at least 0.1, rather than merely a positive value, to reduce the probability of obtaining RF plasticity by chance. In any event, the actual ratio differences were almost always considerably greater than the criterion. The average minimum ratio difference for all cases of RF plasticity was 0.65.

Table 1. RFs across retention periods

Retention period	Number of recordings		
	RF plasticity	No plasticity	Total
1 hr	1	3	4
24 hr	9	11	20
1 week	6	9	15
2 weeks	4	10	14
4 weeks	4	10	14
8 weeks	3	3	6

Retention periods of 1 hr to 8 weeks were used.

RESULTS

Expression of RF Plasticity Under Anesthesia. Fifteen subjects yielded RFs for at least one retention period. Only 4 subjects were tested at 1 hr because of concern about possible retrograde amnestic effects of inducing general anesthesia so soon after training. RFs were obtained from 13 animals at 24 hr and from 9, 10, 9, and 4 subjects at 1, 2, 4, and 8 weeks after training, respectively. A total of 24 (of 35) electrodes provided acceptable posttraining recordings. RF plasticity was obtained in 12 sites (50%) in 9 (60%) subjects. Table 1 summarizes the number of recordings and the number that showed RF plasticity for each posttraining period. Immediate RF plasticity was observed in 1 of 4 (25%) recordings at 1 hr and 9 of 20 (45%) recordings at 24 hr. This difference is statistically significant [χ^2 (df = 1) = 8.0; $P < 0.01$], suggesting that anesthetizing subjects immediately after training may interfere with RF plasticity. The type of anesthetic used had no significant effect on the probability of obtaining RF plasticity (Nembutal, 4 of 7 subjects, 6 of 11 electrodes; ketamine, 5 of 8 subjects, 6 of 13 electrodes; χ^2 values, all $P > 0.05$).

Long-Term Retention of RF Plasticity. Long-term retention was defined as RF plasticity that was present at 1 or 24 hr after training and retained for at least 1 week after training.[§] RFs obtained at 1 or 24 hr and also for 1 week or longer were provided by 20 electrodes (14 subjects). Long-term RF plasticity was found in 10 electrodes (50%; 9 subjects); of the failures, 2 subjects had short-term retention (i.e., 24 hr but not 1 week). Two other subjects exhibited RF plasticity at 24 hr but no acceptable recordings thereafter and so could not be tested for long-term retention. All other subjects that showed RF plasticity at 1 or 24 hr also showed retention at 1 week or longer. The longest duration of plasticity was 8 weeks (Table 1). In all other cases of long-term retention, plasticity was observed for the duration of successful recordings. The type of anesthetic used had no significant effect on the probability of obtaining RF plasticity (Nembutal, 4 of 6 subjects, 4 of 8 electrodes; ketamine, 5 of 8 subjects, 6 of 12 electrodes; χ^2 values, all $P > 0.05$).

An example of long-term retention for 1 week is given in Fig. 1. The pretraining BF was 5.0 kHz, and the CS frequency during training was 10.0 kHz. At 1 hr after training, the pretraining BF exhibited a decreased response, the CS frequency exhibited an increased response, and the BF shifted to the CS frequency. The RF plasticity was retained at 24 hr and 7 days.

Fig. 2 provides an example of long-term retention for >4 weeks. The BF before training was 0.75 kHz and the CS frequency was 1.5 kHz. After training, the response to the pretraining BF was reduced, whereas the response to the

[§]One subject was tested at 1 hr and 2 and 4 weeks; it failed to meet the criterion at 1 hr but showed clear RF plasticity at 2 and 4 weeks. Two subjects were tested at 24 hr and 1, 2, 4, and 8 weeks. Due to a technical problem, data were lost for 24 hr but the criterion of RF plasticity was met at the weekly retention periods. The three subjects were considered to show long-term retention of RF plasticity.

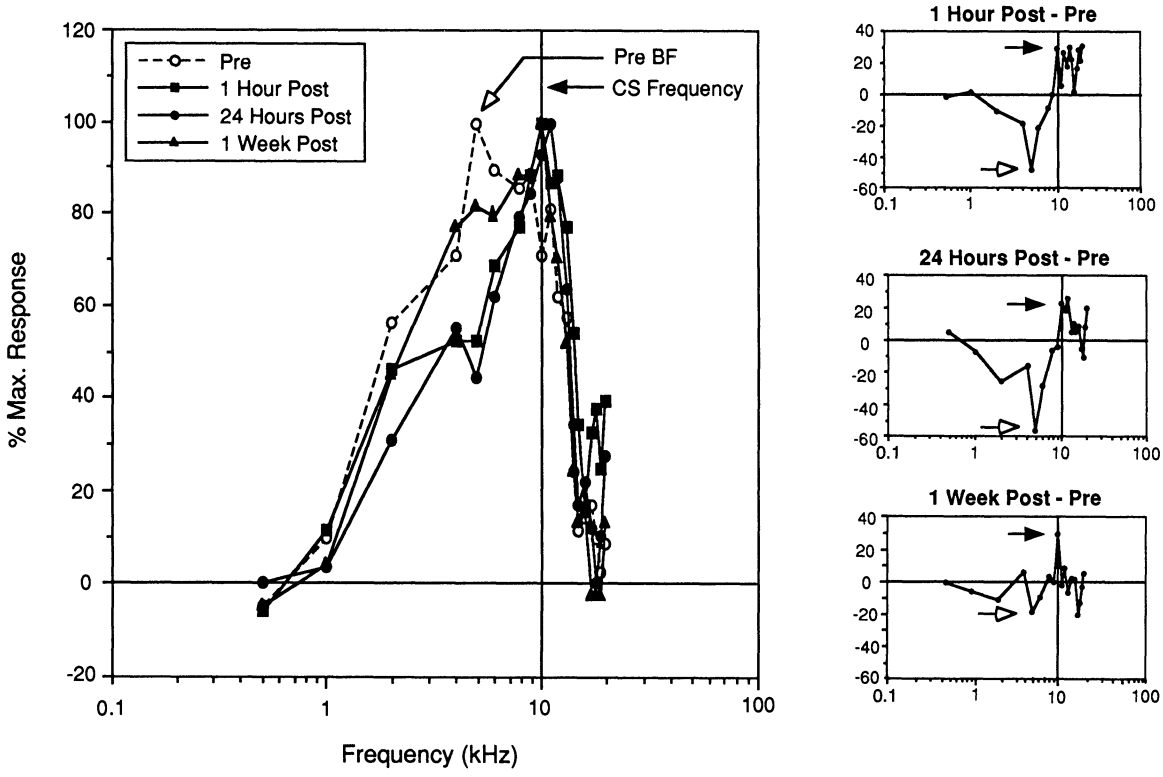

FIG. 1. (*Left*) Frequency RFs (70 dB) illustrating immediate expression and long-term retention of CS-specific RF plasticity and complete shift of tuning. For pretraining, BF = 5.0 kHz and CS = 10.0 kHz. Note the shift of tuning so that the frequency of the CS became the new BF 1 hr after training. The shift was still present 24 hr later; the BF was 11.0 kHz. Long-term retention of the tuning shift is seen at 1 week, which was the final time for which RFs were obtainable; the CS frequency became the BF. (*Right*) Ordinate is percent of maximal response, normalized within a session by expressing response rate to each frequency as percent of response to the frequency that elicited the maximum response; therefore, 100% indicates the BF for each session. Normalization was done because absolute rate of discharge could vary (e.g., ±20%) over sessions as absolute depth of anesthesia may not have been constant. RF difference functions show pronounced decreases at the pretraining BF (open arrows) and increases at the CS (solid arrows) and adjacent higher frequencies. Subject's RFs were obtained under pentobarbital anesthesia.

frequency of the CS was increased. This resulted in a clear shift of tuning so that the CS frequency became the new BF, shown here for both 14 and 32 days after training.

Long-term retention of RF plasticity could be observed not only as a change in frequency tuning but also a reduction in threshold and bandwidth, across intensities, as revealed in

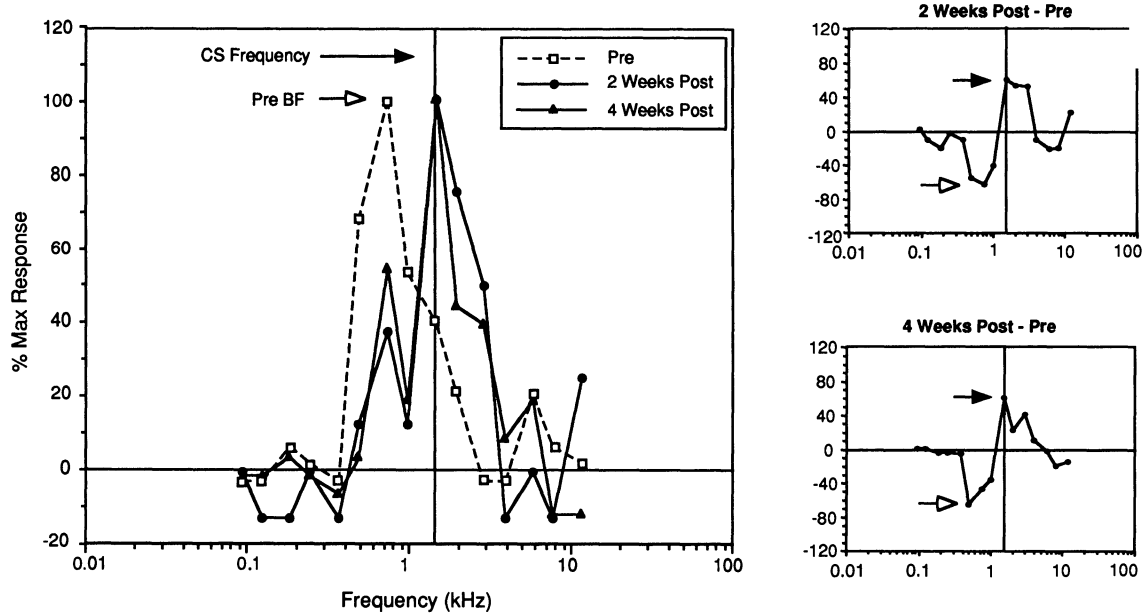

FIG. 2. (*Left*) Frequency RFs (60 dB) illustrating very long-term retention of >4 weeks and complete shift of tuning. For pretraining, BF = 0.75 kHz and CS = 1.5 kHz. Note the shift of tuning so that the CS frequency became the new BF, shown here 2 weeks and approximately 4 weeks (32 days) after training, the last recording available for this subject. (*Right*) Ordinate, same as in Fig. 1. RF difference functions show large decreased responses to the pretraining BF and the largest increases at the CS frequency. Subject was under ketamine anesthesia.

complete response areas (frequency × intensity × rate of discharge). For example, Fig. 3 presents response areas for a recording that showed a partial shift of the pretraining BF toward the CS frequency. For pretraining, the BF was 20.0 kHz; the CS was selected to be 14.0 kHz. At 1 week after training, the BF had shifted toward the CS frequency, to 16.0 kHz. Additionally, the bandwidth of frequency response was reduced and the threshold at 16.0 kHz was reduced ≈20 dB. The shift of tuning toward the CS frequency, the reduction of threshold at 16.0 kHz, and the narrowing of the bandwidth were all retained 4 weeks after training.

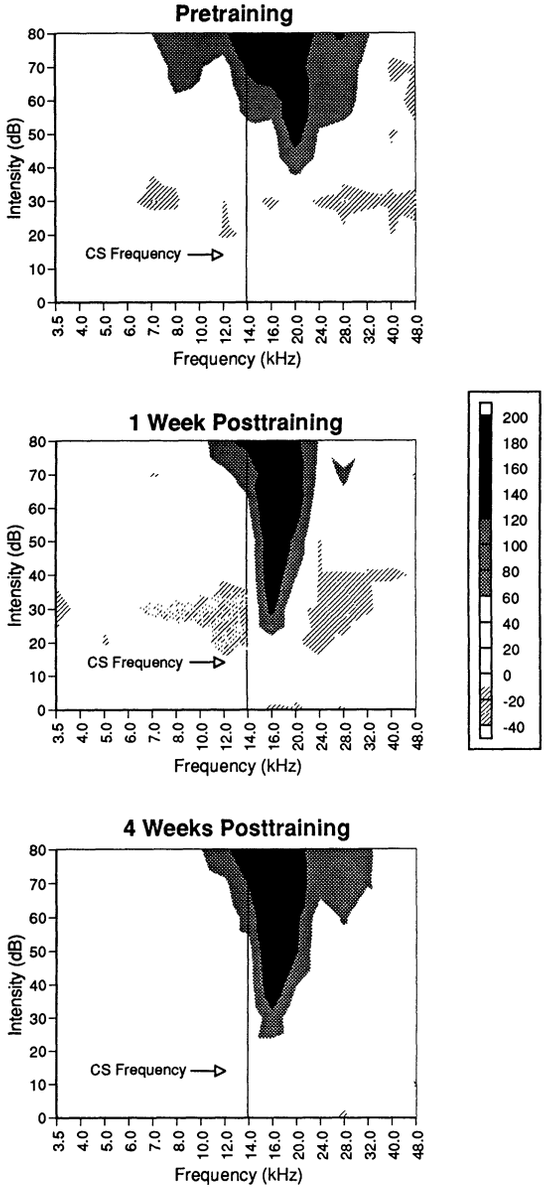

FIG. 3. Expression and long-term retention of RF plasticity across entire response area illustrating a shift of the BF toward the CS frequency and decreases in threshold and breadth of tuning. The abscissa is frequency, the ordinate is stimulus intensity, and shading is rate of discharge (spikes per sec, see scale). (*Top*) For pretraining, the BF was 20.0 kHz, the threshold at BF was ≈40 dB, and the bandwidth conventionally measured 20 dB above threshold was 19.0 kHz (range, 13.0–32.0 kHz). The subject was then trained at 14.0 kHz and the results are shown for the 1- and 4-week retention periods. (*Middle*) At 1 week after training, the BF was shifted toward the CS frequency to 16.0 kHz, the threshold was decreased to 25 dB, and the bandwidth was reduced to 5.5 kHz (range, 14.5–20 kHz). (*Bottom*) These effects were retained 4 weeks after training: BF = 16.0 kHz; threshold = 25 dB; bandwidth = 7.5 kHz (range, 14.5–22.0 kHz). Because of the narrowing of bandwidth, the threshold for the CS frequency (14.0 kHz) actually increased. Thus retuning toward the CS frequency does not always facilitate and can actually reduce responses to this frequency. The subject was under ketamine anesthesia.

The magnitude of change at the CS frequency relative to the BF and the percent change of the CS/BF ratio are summarized in Table 2 for recordings that met the criterion for long-term retention and also for those that did not. The groups differed statistically at 24 hr and 1, 2, 4, and 8 weeks after training. For the long-term retention recordings, the amount of increased response to the CS frequency relative to the BF ranged from ≈50% at 24 hr and 1 week to >300% thereafter.

To determine the amount of shift of the pretraining BF toward the CS frequency, a shift index (SI) was calculated as SI = (posttraining BF − pretraining BF)/(CS frequency − pretraining BF). A value of 0 indicates no shift; a value of +1.0 indicates a shift from the pretraining BF to the CS frequency. RF plasticity does not require any shift of the pretraining BF to another frequency, only that the magnitude of discharge to the CS frequency increases relative to the response to the BF. Nonetheless, there were considerable shifts toward the CS frequency, confined largely to the recordings that developed long-term plasticity. The SI was significantly greater for the long-term retention group than for RFs that did not meet the criterion of RF plasticity at 24 hr and 1, 2, and 4 weeks after training.¶ An SI of 0.5 or greater indicates that the BF shifted at least halfway from the pretraining BF to the CS frequency. A mean SI near or greater than 0.5 was found at all retention periods from 24 hr to 8 weeks (Table 2).

DISCUSSION

The present findings indicate that CS-specific RF plasticity exhibits long-term retention. Although a sensitization control group was not included in this study, CS-specific RF plasticity has been shown to be associative because it requires tone-shock pairing; it never develops in sensitization control subjects (4, 10–12), and develops to the CS^+ (reinforced) but not to the CS^- (nonreinforced) in discrimination training (5, 6). The possible differential effects of arousal on RFs (increase to the CS and decrease to other frequencies) can also be ruled out. Such differential arousal does not occur in waking animals (3, 4) and could not have occurred in this study because RFs were obtained with the subjects under general anesthesia.

We defined long-term retention as CS-specific RF plasticity that was present for at least 1 week. However, retention was considerably longer. RF plasticity was obtained for as long as adequate recordings were obtained, to a maximal retention duration of 8 weeks, the longest period studied. Thus, we have not determined the upper limit of long-term retention.

Recordings were obtained from unit clusters because continuous recordings are not obtainable from single neurons over the very long periods of this study. Therefore, it might be argued that learning did not produce changes in tuning but rather that pretraining and posttraining RFs were obtained from different populations of neurons and that these populations had different tuning. This is extremely improbable for several reasons. (*i*) The shifts could be quite large, e.g., one octave (Figs. 1 and 2). One-octave frequency separations along the frequency axis of the auditory cortex of the guinea

¶The lack of significance at 8 weeks is due to the fact that a subject that previously failed to meet the criterion attained the criterion at 8 weeks, developing a clear shift toward the CS frequency; however, it maintained its nonplastic classification.

Table 2. Magnitude of CS–BF change and SI

Retention period	CS–BF, % change		CS–BF	SI		SI
	Long-term plasticity	No plasticity	*P* value*	Long-term plasticity	No plasticity	*P* value*
1 hr	68.79 (10)	108.73 (9)	NS	0.37 (9)	0.13 (8)	NS
24 hr	49.73 (22)	8.83 (51)	<0.001	0.61 (22)	−0.46 (50)	<0.0001
1 week	50.79 (27)	1.44 (46)	<0.0015	0.82 (27)	−0.19 (45)	<0.0001
2 weeks	294.01 (25)	−1.74 (37)	<0.0004	0.50 (25)	−0.27 (36)	<0.0001
4 weeks	366.60 (22)	16.13 (46)	<0.0001	0.44 (21)	−0.44 (45)	<0.0001
8 weeks	310.55 (12)	86.06 (17)	<0.03	1.26 (13)	0.52 (16)	NS

Retention periods of 1 hr to 8 weeks were used. NS, not significant. Numbers in parentheses indicate the number of RFs that contribute to each mean value.
*Mann–Whitney one-tailed test.

pig are on the order of at least 250–300 μm (13). Thus, to change populations, the microelectrodes would have had to move laterally several hundred micrometers to the CS frequency. There are no known mechanisms for such a displacement nor were there any post-mortem signs of such movement. (*ii*) Shifts of tuning were significantly toward the CS frequency but population changes should also have been equally away from the CS frequency (Table 2). (*iii*) Recordings that met the criterion for long-term retention maintained their RF plasticity for as long as they yielded data, up to 8 weeks. Therefore, population changes would have had to occur only after the pretraining RF but before the 1-week retention test and then not occur for as long as 7 weeks thereafter. In summary, the present findings provide strong evidence for long-term retention of RF plasticity.

The finding that learning-induced RF plasticity is expressed under general anesthesia might be surprising (see also ref. 14). In fact, anesthesia did interfere with RF plasticity when it was induced immediately after training compared to 24 hr after training. However, previous workers have reported RF plasticity in the sensory neocortex of anesthetized subjects caused by chronic sensory deprivation or denervation both during development (e.g., ref. 15) and in the adult animal (e.g., ref. 16). The present finding of retention of RF plasticity under anesthesia suggests that the RFs of sensory cortical neurons under anesthesia might reflect learning experiences in the waking state, whether or not experimenters perform controlled learning experiments. For example, animals subjected to peripheral sensory deprivation either during development or as adults may, as part of their adjustment to a new sensory status, engage in learning as they interact with their environments. Some aspects of either or both developmental and adult sensory cortical plasticity in these cases might reflect such learning in the waking state.

Mechanisms of sensory cortical RF plasticity are under active investigation. It is widely thought that synaptic plasticity underlies RF plasticity and also learning. *N*-Methyl-D-aspartate (NMDA) receptors have been implicated in synaptic plasticity (17–20). NMDA receptors may be necessary for RF plasticity because blockade of NMDA receptor activation interferes with the induction of RF plasticity during development (21–23) and in the adult (24). Ketamine blocks NMDA receptors (25). In the present study, RF plasticity was expressed under ketamine (as well as barbiturate) anesthesia, suggesting that interference with NMDA receptors does not prevent the expression of learning-induced RF plasticity in the auditory cortex. The role of NMDA receptors in the induction of learning-induced RF plasticity remains to be studied.

The present finding of long-term retention of CS-specific RF plasticity in the primary auditory cortex completes a basic characterization of this phenomenon, which is associative, rapidly induced, highly specific, and discriminative. Together, these characteristics constitute criteria for the long-term storage of learned information in the auditory cortex. It has been proposed that sites of memory storage may exist at sites of stimulus analysis (26). The present findings are consistent with this proposal.

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