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Sensitization induced receptive field plasticity in the auditory cortex is independent of CS-modality

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Sensitization training with an auditory stimulus produces a general increase in response magnitude across the entire receptive field (RF) of neurons in the primary auditory cortex of the guinea pig (Bakin, J.S. and Weinberger, N.M., *Brain Res.*, 536 (1990) 271–286). To determine if this effect reflects an auditory system-specific process or is caused by a process independent of the training stimulus modality, RFs in primary auditory cortex were characterized before and immediately after adult guinea pigs were given sensitization training with either an auditory or a visual training stimulus. General increases in auditory response magnitude across the RF were observed in 7 out of 7 auditory sensitization cases and 4 out of 5 visual sensitization cases. There were no statistical differences between the effects of auditory and visual sensitization training. These findings indicate that the general increases observed following sensitization training are the result of processes independent of CS modality, in contrast to the highly specific RF modifications that are caused by classical conditioning. The findings suggest that the 2 forms of RF plasticity, CS-specific re-tuning due to associative conditioning and polymodal general increases in gain due to non-associative sensitization, may reflect neural mechanisms involved in selective attention and vigilance, respectively.

INTRODUCTION

Learning alters the signal value of sensory stimuli. In the most extensively studied situation, Pavlovian ('classical') conditioning, an acoustic conditioned stimulus (CS) which precedes an aversive unconditioned stimulus (US) produces rapidly acquired (e.g. 5–10 trials) autonomic and general somatic conditioned responses (CR) and more slowly acquired (e.g. 60–200 trials) specific somatomotor CRs to CS presentation. The rapidly-developing CRs are thought to index a central state of acquired fear to the CS whereas the more slowly acquired CRs may constitute skilled motor responses which attempt to avoid or remove the US^{17,19,23,26–30}.

A fundamental and enduring issue has been the extent to which the behaviorally expressed, acquired modification of CS signal value is based upon an actual *alteration of sensory coding and processing of CS information within the CNS*. Although contrary to common sense (an imperfect guide at best), an extensive literature has established that neural responses to the CS are increased within its sensory system as it becomes a signal for the forthcoming US^{15,18,21,31}. The findings apply to all sensory systems but have been investigated most extensively for the auditory system. Sensitization controls (unpaired CS and US) and discrimination par-

adigms have established that this type of sensory system plasticity is caused by associative processes³¹.

Nonetheless, these findings are insufficient to resolve the issue. Learning might involve a *general increase in responsiveness ('gain')* to all acoustic stimuli, or it might specifically alter processing of CS information alone, i.e. a *specific change in auditory system 'tuning'*. Both processes would produce the observed increased response to the frequency of the CS, and thus cannot be distinguished unless responses not only to the CS but to all stimuli within the neuron's receptive field (RF) are determined. If learning merely increases 'gain', then responses to other stimuli as well as the CS would be facilitated. However, if learning actually modifies the way that CS information is processed and represented, then it should specifically increase responses to the CS while decreasing or having less of an effect on responses to stimuli other than the CS.

The first application of receptive field analysis to associative learning found strong support for plasticity of receptive field tuning of neurons in cat secondary auditory cortical fields. Frequency RFs from single neurons were obtained before and following conditioning with a single tone; post-training RFs showed a systematic change in tuning, e.g. responses to the frequency of the CS were increased whereas responses to other frequen-

cies were decreased^{3,4}. More recently, we extended this type of study to the primary auditory cortex of the guinea pig and again found that associative processes induced specific changes in tuning, including a shift in the RF's best frequency (BF, the frequency that evokes the greatest response at a given intensity) to match the frequency of the CS. Moreover, CS-specific re-tuning was present at the longest retention interval tested (24 h)¹.

These findings reveal that associative learning can produce specific re-tuning of receptive fields. But there are also circumstances in which a general increase in responsiveness, i.e. an increase in 'gain', is induced by experience. Sensitization training (unpaired presentation of a tone and shock) causes a general increase in response magnitude across the frequency receptive field^{1,2}. In other words, fundamentally different types of experience invoke different types of receptive field plasticity—re-tuning due to conditioning (associative learning) and general increased responsiveness due to sensitization training (non-associative learning).

Although sensitization training is viewed mainly as a control for associative learning, the process of sensitization itself has been the subject of intensive neurobiological inquiry⁹. In the present case, we sought a better understanding of sensitization effects on auditory cortical receptive fields. It might be assumed that general increased response across frequency RFs in the auditory cortex is modality-specific, because this process was discovered when an auditory stimulus was presented unpaired with an US. However, it is possible that this general 'gain' change develops regardless of the modality of stimuli present during sensitization training, i.e. that it reflects polymodal processes. To resolve this issue, we studied sensitization-induced RF plasticity in the auditory cortex in which either a visual or an auditory stimulus was presented unpaired with an unconditioned stimulus. Some of these findings have been reported in preliminary form².

MATERIALS AND METHODS

Most aspects of the materials and methods are identical to those used previously¹. What follows are detailed descriptions of the unique features of this study and brief descriptions of the basic materials and methods involved.

Experimental design

Guinea pigs were implanted with chronic indwelling electrodes in primary auditory cortex. After characterization of pre-training auditory receptive fields, the subjects were assigned to one of two groups: sensitization training with an auditory stimulus (AudS) or sensitization training with a visual stimulus (VisS). Subjects were placed in the training apparatus and allowed to habituate to the new surroundings for 15 min. Sensitization training was then initiated. Immediately after training, the subjects were returned to the original acoustic chamber, and the receptive fields were re-characterized to determine the effects of both types of training on RFs.

The entire experiment lasted about 3.5 h (approximately 30 min each for the pre- and post-training RF determinations, 1 h for behavioral training, and 15 min for each transition between acoustic chambers).

Subjects and surgery

Twelve adult male Hartley guinea pigs (350–600 g, Hilltop Farms) were anesthetized (atropine sulfate 0.02 mg/kg, diazepam 8 mg/kg, sodium pentobarbital 20 mg/kg) and prepared for sterile surgery. A craniotomy was performed over the left auditory cortex and an electrode array consisting of 10 formvar-coated tungsten wires (0.002 in. California Fine Wire Company; electrodes spaced 300 μ m apart, impedance approximately 3–10 M Ω 1 kHz) was advanced radially under electrophysiological control. After attainment of large evoked potentials on a majority of electrodes, the array was cemented in place (mean depth 1176 μ m, range 1000–1500 μ m). Animals recovered in an incubator.

Recording sessions and receptive field determinations

The unanesthetized animal was restrained by a hammock held within a metal frame located inside an acoustic chamber. Its pedestal was bolted to a rigid post, and a calibrated speaker was placed against the opening to the contralateral ear canal. Recording sessions lasted approximately 30 min. Guinea pig heart rate shows adaptation and stability in this situation⁵.

Electrodes were monitored every few days for signs of tone-evoked discharges. If an electrode revealed satisfactory discharge characteristics (identifiable waveforms, 3:1 signal-to-noise ratio or better), then the receptive field was characterized. A computer-controlled digital frequency synthesizer generated an iso-intensity ascending frequency series of tone bursts (50 ms duration, inter-tone interval 550 ms, rise–fall 5 ms). The frequencies used covered the range of responsiveness for the particular neuronal cluster recorded. Therefore, the frequencies used varied across animals but were constant for a given animal across its recording sessions. The auditory response to sets consisting of 20 repetitions of these iso-intensity frequency series were determined at 10 dB intervals beginning at threshold and covering a range of at least 50 dB, or until the auditory response was saturated.

Neuronal activity was amplified, filtered (300–3000 Hz), voltage-discriminated, monitored on a storage oscilloscope, and recorded on analogue tape. A laboratory computer stored the times of occurrence of action potentials (voltage detector pulses) and stimuli, and was used for quantitative data analysis and to construct peristimulus–time histograms. Great effort was used to insure waveform constancy before and after training. First, only clusters consisting of few waveforms (mean less than 4) with signal to noise ratios of 3:1 or greater were included. Second, the amplitude of the post-training cell population had to be similar to that of the pre-training cell population, as the spike level discriminator was kept constant once set prior to the beginning of the pre-training RF determination. Third, post-training waveforms were compared to photographs of pre-training waveforms and any subject whose post-training recording suggested that the waveform population had changed was eliminated from further consideration.

Sensitization training

Behavioral training was performed in an acoustic chamber distinct from the recording chamber. Animals were placed in a plexiglass box with perforated sides and a grid floor (12 in. high \times 10 in. wide \times 5 in. deep). An 8 in. speaker and a strobe light (Realistic RS-42-3009A) were attached to the walls of the acoustic chamber. A small amount of electrode cream (Bendix EKGsol) was applied to the paws. The chamber was dimly illuminated by a low level ceiling light, and air flow was maintained by a wall fan.

The auditory stimulus for AudS subjects was a 10 s, 80 dB tone. The frequency of the tone was determined by inspection of the pre-training receptive field. It had to be an effective stimulus but not be the best frequency (BF) at more than one intensity. The visual stimulus for VisS subjects was a 10 s period of 2 light flashes

per s. For both AudS and VisS, the US was a 2 s constant current footshock (1–4 mA) delivered through the chamber's grid floor. Sensitization training consisted of presentations of either the auditory or the visual stimulus and were explicitly unpaired with US presentations. Each animal received one training session consisting of 30 trials of each stimulus presented in random order (mean interstimulus interval 60 s, range 30–90 s, total training time 66 min). Strictly unpaired presentation of the CS and US were used instead of random presentation because associative fear conditioning might occur with only a single trial in which the CS preceded the US closely in time. Although a negative contingency between the CS and US can be learned with unpaired presentation²⁵, this requires a much larger number of trials than were presented in this experiment^{10,11}.

Quantification of neuronal data

Frequency receptive fields were calculated by subtracting the average discharge during the pre-tone period (500 ms) from the average discharge during each tone*, thus obtaining a measure of tone-evoked activity. This method accounts for general effects on background activity. The evoked response to the 20 presentations of each tone was averaged for each intensity and plotted vs. frequency. Evoked response across the frequency dimension constitutes the receptive field (RF). RF difference functions revealed the effect of training, and were calculated by subtracting the pre-training RF from the post-training RF of the same intensity. Comparisons across animals and group means were made on normalized difference scores. In order to equally weight the contribution of each animal's difference score, all group means were based on percentage change from pre-conditioning baseline receptive fields. A percentage difference score response function was calculated by dividing the difference score of each frequency by the absolute value of the largest difference score obtained for a frequency within that same iso-intensity set. This result was multiplied by 100 for a percentage value

Normalized difference score =

$$\frac{\text{Difference score}}{\text{Maximum difference score}} \times 100.$$

For each training session, the dominant effect was classified as increase, decrease or no change. In order to determine the dominant effect for a session, each RF difference function was characterized by counting the number of frequencies that increased, decreased or did not change response following training. A change in response was defined as any increase or decrease that was greater than 5% of the largest absolute value difference score exhibited during the same RF difference function (see above). For example, a RF difference function could be described as '8,1,3', indicating that responses to 8 frequencies increased, 1 did not change and 3 decreased. These individual RF difference function totals were summed across all intensities within each session. For instance, if responses to 4 iso-intensity series of 11 frequencies were tested, the overall receptive field difference function could be recorded as 27, 10, 7, totaling 44 tones. Each animal was then classified according to the largest total. Thus, a difference function total of '27,10,7' would be classified as an increase.

The single intensity RF difference that showed the maximal effect for the classification was used to compute a group RF difference function. Because different frequency ranges were used for different subjects, a common frequency reference was established using an octave scale. Frequencies were grouped and averaged according to quarter octave intervals across the range of ± 1.5 octaves centered at the CS or the pre-training BF. Additional statistical

evaluations were based on all of the data across all intensities, as explained in the Results.

Recording sites in auditory cortex

The auditory cortex of the guinea pig consists of 3 tonotopic fields plus several surrounding non-tonotopic fields aligned in a rostral-caudal direction²⁴. Tonotopic fields A and DC receive projections from the tonotopic auditory thalamus nucleus, the ventral medial geniculate. In the present experiment, examination of best frequencies along the rostral-caudal dimension within an electrode array revealed that recordings were obtained from the largest field (A). Some recordings from posterior electrodes were likely to have been obtained from field DC, but in the absence of a detailed frequency map, no firm conclusion can be drawn. 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 record from tonotopic auditory fields, the absence of clear attribution of each recording site either to field A or DC is not a severe limitation.

RESULTS

Behavior

Animals were observed through a window in the acoustic chamber for the entire duration of training. All animals displayed orienting responses to the sensitization stimulus (tone or flashing light) that habituated during training. Behavioral responses observed during training trials included chewing, freezing, head movement and rearing. No consistent expression of these behaviors was observed during the course of sensitization training, in contrast to conditioning¹.

Neuronal data

Prior to training, the subjects assigned to the auditory ($n = 7$)** and visual ($n = 5$) sensitization groups were not significantly different with respect to best frequency (Mann-Whitney, $U = 13$, $P > 0.05$), intensities tested ($U = 293.5$, $P > 0.05$) or the range of intensities tested ($U = 17$, $P > 0.05$).

Out of 12 subjects 11 exhibited general increases in response magnitude across the entire RF following sensitization training. This percentage of increased responses was significantly different from chance (Binomial test, $P < 0.003$). The general increases will be discussed separately according to treatment group: auditory or visual sensitization.

Auditory sensitization

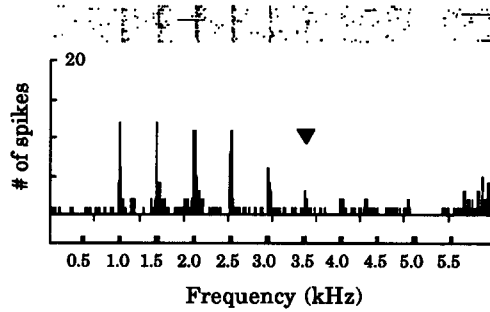
Auditory sensitization training produces a general increase in response magnitude across the RF. An example is illustrated in Fig. 1. Prior to sensitization training, the RF was 1.0–4.0 kHz. Immediately following training

* Average tone discharge was calculated for a time window set to frame the evoked response, usually 10 to 40 ms after tone onset.

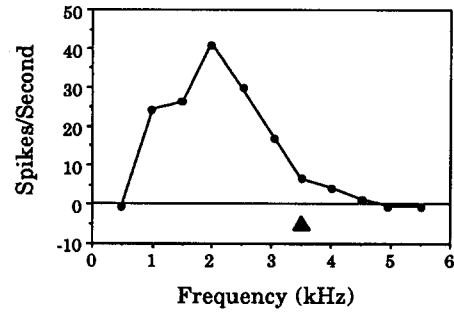
** The data from 3 AudS subjects was obtained from a previous study¹. Four additional AudS subjects and all 5 VisS subjects were prepared for this experiment.

Auditory Sensitization

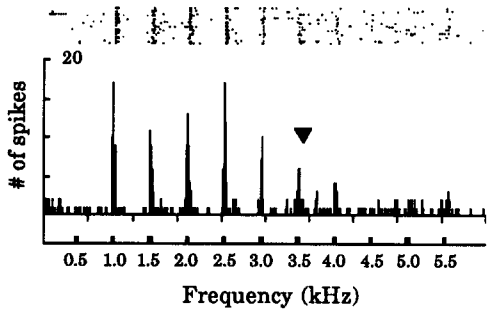
A. Pre PSTH



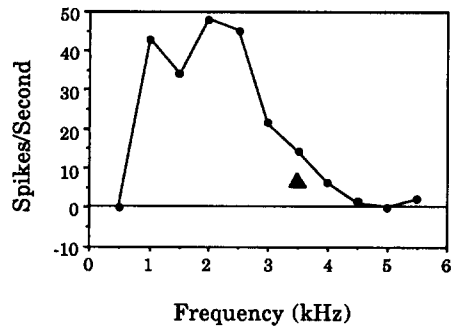
B. Pre RF



C. Post PSTH



D. Post RF



E. Post RF minus Pre-RF

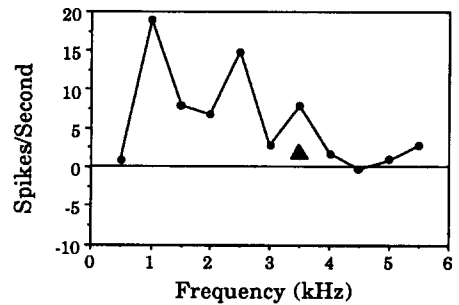


Fig. 1. Auditory sensitization produces a general increase in receptive field responses. Prior to sensitization training, this cluster was responsive to low frequencies (1.0–4.0 kHz) as evidenced by the pre-training peristimulus histogram (PSTH; A) and quantified pre-training receptive field (B). Following 30 trials of unpaired presentations of a 3.5 kHz stimulus (▲, ▼) and a 2 s footshock, the response magnitude of the RF was greatly increased across many frequencies (1.0–4.0 kHz; C,D). The effect of sensitization training is revealed by subtracting the pre-training RF from the post-training RF and is plotted as the RF difference function (E). Note the general increase in response magnitude across the entire frequency range (●).

with a CS of 3.5 kHz, there was a large increase in evoked activity across the RF. This increase was not due

to an overall state change as the background activity was unaffected.

Sensitization versus Conditioning

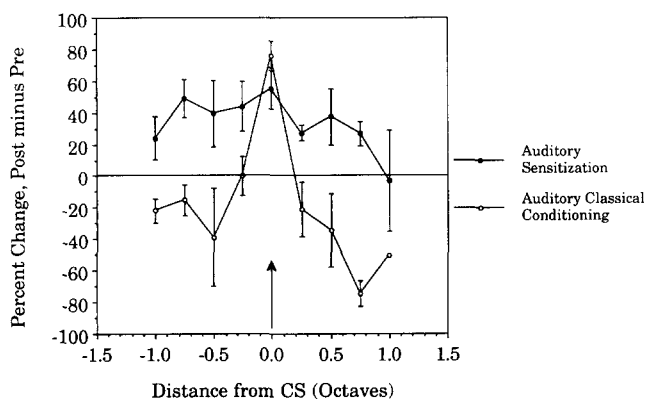


Fig. 2. Comparison of the effects of conditioning and sensitization on auditory cortex receptive fields. Group receptive fields difference functions for classical conditioning ($n = 7$; \circ) and auditory sensitization ($n = 7$; \bullet) reveals that while both treatments increase responsiveness at the frequency of the CS (arrowhead), they differ in the overall effect on the receptive field. Conditioning produces a highly specific increase in the receptive field such that only the frequency of the CS is increased while the responses to other frequencies are decreased. In contrast, sensitization training with an auditory CS produces a broad-band increase in response magnitude across a large frequency range. This figure illustrates the value of characterizing the entire RF: otherwise, the difference between classical conditioning and sensitization would be considered to be quantitative, rather than both qualitative and quantitative (conditioning data from our previous report¹).

Out of 7 animals given AudS training, 7 exhibited this general increase (Binomial test, $P < 0.008$). The average change in frequency tuning is presented in Fig. 2. Note the lack of specificity with respect to frequency and the general increased response of approximately 45%. To contrast sensitization effects with conditioning effects, Fig. 2 also presents the average RF difference function for CS frequency-specific modification due to classical conditioning¹. Note the increase at the CS frequency and the decreased responses at other frequencies. Although both types of training produce increased responses at the CS frequency, they produce opposite effects at other frequencies. Thus, conditioning produces CS-specific RF plasticity (i.e. re-tuning), whereas sensitization produces a general increase in response (i.e. increase in 'gain'). A test of the present sensitization effects with the previous conditioning effects indicates significant differences with respect to both group and frequency factors (ANOVAs: groups $F_{1,61} = 37.9$, $P < 0.0001$; frequencies, $F_{8,61} = 6.2$, $P < 0.0001$; group \times frequencies, $F_{8,61} = 2.5$, $P < 0.0182$).

Visual sensitization

Sensitization training with a visual stimulus also produces general increases in frequency receptive fields.

This was found in 4 of 5 subjects; 1 subject yielded a general decrease. One case is illustrated in Fig. 3. Prior to VisS training, the cells were responsive to frequencies from 1.0–10.0 kHz. Immediately following training, the response magnitude was greatly increased across the RF. This increase was not due to a non-specific change in state as the background activity did not increase.

The group average of the RF changes for the VisS increases is given in Fig. 4, together with the AudS group average. In order to compare visual and auditory sensitization effects, a common reference point was needed. Because the visual sensitization animals did not receive an auditory CS, it was not possible to use that as the comparison frequency with auditory sensitization. Therefore, the BF, i.e. the frequency evoking the greatest pre-training response, was used as the reference frequency.

First note that as expected, the general increase due to auditory sensitization that is present with respect to the CS (Fig. 2) is also evident when expressed with respect to the BF. This demonstrates that the AudS general increase is indeed a general effect across the RF. Second, note that there is no difference in magnitude or bandwidth of the effects between AudS and VisS groups. Both functions exhibit an increase of approximately 45% across the frequency RF, covering ± 1 octave with respect to the BF. Statistically, there was no difference (ANOVA: groups, $F_{1,46} = 0.761$, $P > 0.3877$; frequencies, $F_{8,46} = 0.622$, $P > 0.7552$; groups \times frequencies, $F_{8,46} = 0.339$, $P > 0.946$).

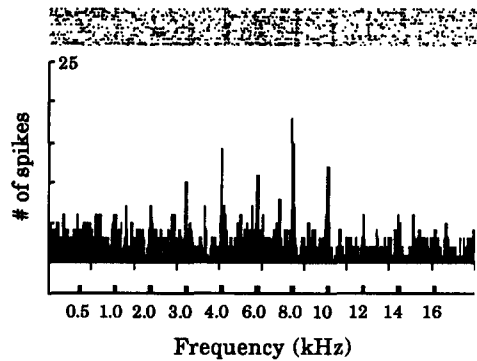
The lack of difference applied to all of the data, as well as to the maximal effects. First, there was no difference in the mean increase at the BF across all intensities ($t_{10} = 0.93$, $P = 0.37$). Second, the likelihood of an increased response to any frequency was not significantly different for the 2 groups: AudS, 72.76% VisS, 76.74%, ($t_{50} = 0.60$, $P = 0.55$).

DISCUSSION

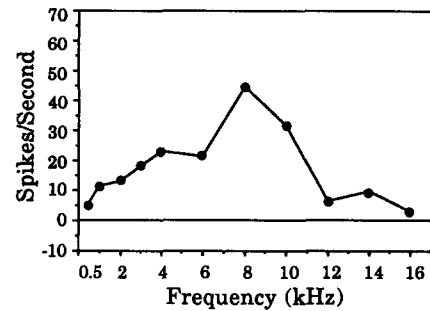
This study has two main results. First, extending a previous report¹, sensitization training with an auditory stimulus produces a general increase in responses across the receptive fields of neurons in the auditory cortex. Second, sensitization training with a visual stimulus also produces a general increase in RF response magnitude that is indistinguishable from the effect of sensitization with an auditory stimulus. These findings demonstrate that the mechanisms by which sensitization training modifies the processing of acoustic stimuli at the auditory cortex are polymodal, i.e. they are not limited to the modality of the training stimulus. The discussion that follows will cover the validity of the results, their relationship to previous findings, and the possible functional

Visual Sensitization

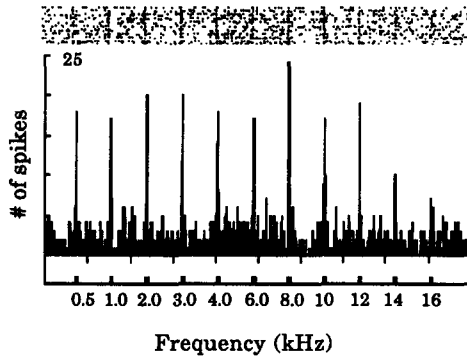
A. Pre PSTH



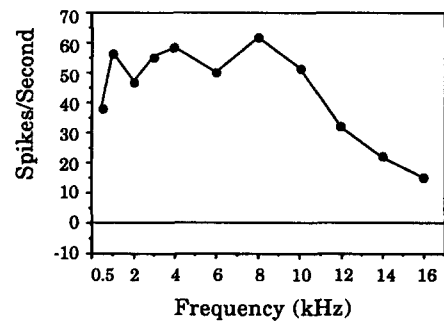
B. Pre RF



C. Post PSTH



D. Post RF



E. Post-RF minus Pre-RF

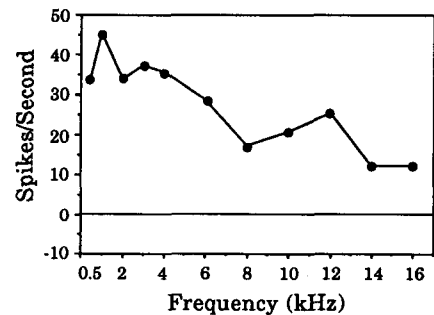


Fig. 3. Visual sensitization produces a general increase in auditory cortex receptive field tuning. Pre-training PSTH (A) and quantified receptive field (B) reveal auditory responses between 1.0 and 14.0 kHz. C,D: following sensitization training with a visual CS, this cluster responded strongly from 1.0 to 16.0 kHz. E: the effect of visual sensitization training on auditory receptive fields is quantified in the RF difference function. Note the general increase in response magnitude across the entire RF.

significance of the effects of sensitization training.

Validity of results

General increases in response magnitude might result

from several non-interesting variables. One explanation would be a change in the population of cells recorded during RF characterizations resulting in non-valid RF descriptions. It might be that the pre-training population

Auditory versus Visual Sensitization

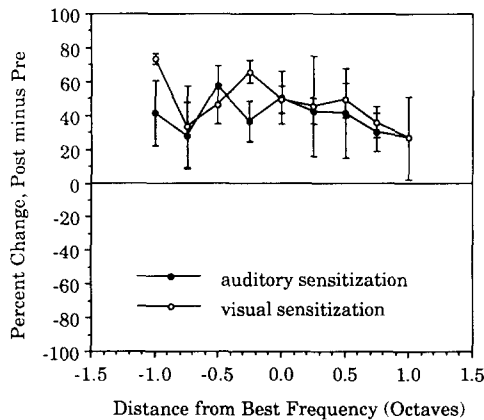


Fig. 4. Group RF difference functions for auditory and visual sensitization. Comparison of the effect of visual (○) and auditory (●) sensitization on auditory cortex RF tuning. Data have been normalized for response magnitude and cluster frequency response range. Note that the X-axis is distance in octaves centered around the cluster best frequency. Both auditory and visual sensitization training produce large increases in RF response magnitude. Auditory sensitization produced general increases across the RF in 7 out of 7 subjects. Visual sensitization training increased auditory cortex RF response magnitude in 4 out of 5 subjects: the average increase of those 4 cases is plotted here.

was somehow lost, a new post-training population replaced it, and the new population was more responsive to tones than the pre-training population. This is extremely improbable. As pointed out in the Methods, we exercised great care in monitoring waveform constancy and excluded any suspect data. Moreover, if the results were due only to a change in the post-training cell population, then both increases and decreases should occur with the same probability, but this was not the case as 11/12 cases developed a general increase in response. Finally, the possibility that the results are due only to the nature of the recording technique seems unlikely because the identical technique was used in the previous report of conditioning which described highly specific modifications of RFs¹. This suggests that the differences in RF modifications observed between the two studies are the result of the differences in the training paradigms.

A second explanation would be an increase in post-training stimulus intensity due to a change in speaker location during the post-training RF determination. This is unlikely as extreme care was taken to return the speaker to its original location. Further, the speaker could not be moved closer to the animal because it was placed against the external auditory meatus. Moreover, large threshold shifts, which would indicate a simple change in stimulus intensity, were not typically observed. Finally, the same speaker placement was used in the

previous study of conditioning, in which frequency specific RF changes were found¹.

It might be thought that subjects were more tonically aroused in the post-training session and this increased arousal might account for the increase in evoked responses. However, general increased responses were often observed in cases where there was no increase in background activity (e.g. see Figs. 1 and 3). It might be argued that phasic arousal to presentation of the CS frequency could account for increased responses to that frequency and those presented immediately following the CS frequency during RF determination. Inspection of the rasters and histograms of the individual cases did not reveal such a pattern of increased responses to a limited number of frequencies near the CS frequency. In addition, this could not account for the changes observed following visual sensitization, as the visual CS was never presented during RF determination.

Relation to previous studies of sensitization effects on receptive fields

Changed responses across the RF have been seen previously in the auditory cortex of the cat following sensitization training with an auditory CS³. In that study each subject underwent sensitization training prior to classical conditioning training; some of these subjects developed general RF increases following sensitization training but the authors did not systematically characterize those changes. Recently, the effects of auditory sensitization training on thalamic RFs have been described in the guinea pig. Sensitization training produces general increases in RF response magnitude and this effect is seen in all 3 major subdivisions of the medial geniculate body, the dorsal, ventral and medial divisions⁵⁻⁷. Thus, sensitization training produces general increased responses in frequency RF in the auditory thalamus as well as in the auditory cortex. Understanding the extent to which these 2 levels of the auditory system interact during sensitization will require further experiments. Likewise, whether sensitization training with a non-auditory CS also has the same effects in the auditory thalamus as at the auditory cortex remains to be investigated.

RF analysis resolves several long-standing objections to learning-induced modification of auditory system processing

Characterization of the effects of classical conditioning, auditory sensitization and visual sensitization on the receptive fields of auditory cortical cells has enabled the resolution of 2 long-standing objections to the conclusion that learning can specifically modify the processing of auditory information. The core arguments are:

- (1) Both visual and auditory conditioning produce in-

creased auditory responses; therefore increased responses reflect non-auditory system processes and learning has no effect on the auditory system per se.

(2) Both sensitization and classical conditioning produce increased responses to the frequency of the CS; therefore modification of auditory system processing is due to non-associative processes and not to associative learning.

The assumptions and data supporting each of these objections will be briefly summarized, and the role of RF analysis in refuting each criticism will be elaborated.

Classical conditioning with visual and auditory stimuli. Mark and Hall²⁰ found that the magnitude of click-evoked potentials increased after a subject acquired a CR to a click CS^{13,20}. However, they also found increased evoked potentials to irrelevant clicks presented to subjects during acquisition of a visual CR. They concluded that the increased auditory response could not have reflected the specific association between the auditory click stimulus and the unconditioned stimulus. Rather, they concluded that increased responses must have reflected fear, which they thought was common to both training experiences¹³.

This objection rests on the assumption that the same observation, when generated under 2 different circumstances, must have the same underlying mechanism. Thus, if increased responses to irrelevant clicks occur following visual conditioning, then when increased click responses occur following auditory conditioning, they cannot reflect the learned association between the click CS and the US. This conclusion is no longer tenable because of the differences observed in RFs between auditory conditioning on the one hand and auditory and visual sensitization on the other hand. Although all 3 training procedures produce increased responses to the frequency of the CS, auditory and visual sensitization also increase responses across the RF, whereas conditioning decreases responses to non-CS frequencies (Figs. 2 and 4). Thus, measuring only the response to the frequency of the CS cannot reveal the different effects of conditioning vs. sensitization.

We believe that the CS-specific increase is due to the predictive value of the CS regarding the US. In the absence of this acquired association, general increases across the RF result due to the presence of a noxious US, as observed for both auditory and visual sensitization. Hall and Mark²⁰ studied only visual conditioning, not sensitization. However, we predict that visual conditioning and visual sensitization would have the same effect, i.e. a general increase of responses for auditory RFs, because of the lack of an auditory stimulus that predicts the US. Visual conditioning might well cause highly specific visual RF plasticity in the visual cortex.

Sensitization and classical conditioning. A second objection to the hypothesis that learning specifically alters auditory system processing is that non-associative processes could account for the changes observed during conditioning¹⁶. Without characterizing the RF, it might be concluded that sensitization and conditioning produce similar changes to the frequency of the CS. If so, then the changes produced by conditioning would be considered trivial in light of the non-associative changes produced by sensitization training. That is, it could be argued that the increases are due only to processes activated by the presentation of strong unconditioned stimuli.

However, RF analysis eliminates this objection. As we have shown, sensitization and conditioning produce qualitatively different effects across the RF, not merely increases at the frequency of the CS. Thus, the effects of associative learning produced by conditioning cannot be explained by the non-specific increases produced by non-associative sensitization training.

RF analysis reveals that sensitization is qualitatively different from classical conditioning

Prior to the use of RF analysis, the majority of investigations into the mechanisms of sensitization, whether using electrophysiology, metabolic assays or biochemistry, have concluded that conditioning and sensitization produce qualitatively similar results that differ primarily in magnitude. For example, the average response to the CS of single cells in motor cortex is significantly increased following sensitization, but the increase is smaller than that found following conditioning²². In addition, both classical conditioning and sensitization training significantly increases 2-deoxyglucose uptake in the auditory cortex when compared to naive controls, but classical conditioning produces a significantly greater uptake than does sensitization training¹². The similarity in the biochemical mechanisms of sensitization and classical conditioning in the mollusc *Aplysia* have led investigators to hypothesize that 'classical conditioning and sensitization are not fundamentally different, as is frequently thought, but rather the cellular mechanism of conditioning appears to be an elaboration of the mechanism of sensitization'¹⁴.

However, conditioning-induced frequency-specific auditory cortical RF plasticity probably cannot arise from sensitization processes. First, auditory conditioning training produces effects which are qualitatively different from those produced by auditory sensitization training. Conditioning produces highly specific changes within the frequency dimension, e.g. increased response to the CS frequency, with decreased responses to non-CS frequencies. In contrast, auditory sensitization training produces a

general increase in response magnitude across the frequency dimension. Thus, the increased response at the CS due to conditioning is not merely a facilitated sensitized response.

Second, the present findings establish that sensitization effects are polymodal, i.e. visual sensitization training produces the same general increased responses to auditory stimuli as found with auditory sensitization training. This equivalence would seem to rule out sensitization as the basis for conditioning-induced RF plasticity in auditory cortex. To argue that unimodal conditioning processes are fundamentally the same as polymodal sensitization processes, one would have to argue that frequency-specific auditory plasticity could arise from the processes of visual sensitization. Yet no auditory stimuli are present during visual sensitization training and consequently there is no possible learning about acoustic frequencies in this situation. As there is no learning about acoustic stimuli, there can be no specificity of plasticity in frequency receptive fields. In summary, both within modality and cross-modality data would appear to eliminate sensitization processes as the basis for frequency-specific auditory cortical RF plasticity.

Possible functions of increased responses induced by sensitization

Behaviorally, 2 types of altered processing of sensory stimuli have been recognized within the field of attention: selective attention and vigilance⁸. Selective attention refers to facilitated processing of a specific, limited subset of all stimuli such that non-attended stimuli receive less of the processing resources of the brain. This may be indexed as improved recognition of a target stimulus with reduced recognition of other stimuli. Selective attention is particularly effective when the organism has previously learned the characteristics of a particular stimulus and this stimulus is likely to occur in the cur-

rent situation. Vigilance refers to facilitated processing of sensory events in general and may be indexed as decreased reaction time to stimuli in any modality.

The 2 types of receptive field plasticity, CS-specific re-tuning following associative learning and polymodal general increases in sensory gain following sensitization training, may be part of the neural substrates for selective attention and vigilance, respectively. Neural processes that favor the CS would appear to be adaptive for predicting the US, and for more complex processing based upon the presence of the CS. These processes, promoted by the associative learning of the specific relationship between a CS and a US, could provide the neural basis for selective attention. In contrast, a state of heightened vigilance, in which facilitated responses to stimuli across modalities would facilitate behavioral responses (e.g. as in the case of stimuli produced by potential predators, conspecifics, etc.), might be promoted by increased sensory neuronal responses to stimuli across modalities. The facilitated responses in primary auditory cortex receptive fields seen in this study with both auditory and visual sensitization training would be an example of neural mechanisms operative in vigilance. If this is the case, then we would expect facilitated responses across the receptive fields of neurons within all sensory systems to be observed following sensitization training with stimuli from any sensory modality, a complete polymodal mechanism resulting in receptive field plasticity. These predictions are subject to experimental test.

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