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Learning-Induced Physiological Memory in Adult Primary Auditory Cortex: Receptive Field Plasticity, Model, and Mechanisms

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Adult plasticity
Representation of frequency
Basal forebrain cholinergic system
Hebbian mechanisms

Abstract
It is well established that the functional organization of adult sensory cortices, including the auditory cortex, can be modified by deafferentation, sensory deprivation, or selective sensory stimulation. This paper reviews evidence establishing that the adult primary auditory cortex develops physiological plasticity during learning. Determination of frequency receptive fields before and at various times following aversive classical conditioning and instrumental avoidance learning in the guinea pig reveals increased neuronal responses to the pure tone frequency used as a conditioned stimulus (CS). In contrast, responses to the pretraining best frequency and other non-CS frequencies are decreased. These opposite changes are often sufficient to shift cellular tuning toward or even to the frequency of the CS. Learning-induced receptive field (RF) plasticity (i) is associative (requires pairing tone and shock), (ii) highly specific to the CS frequency (e.g., limited to this frequency ± a small fraction of an octave), (iii) discriminative (specific increased response to a reinforced CS+ frequency but decreased response to a nonreinforced CS– frequency), (iv) develops extremely rapidly (within 5 trials, the fewest trials tested), and (v) is retained indefinitely (tested to 8 weeks). Moreover, RF plasticity is robust and not due to arousal, but can be expressed in the deeply anesthetized subject. Because learning- induced RF plasticity has the major characteristics of associative memory, it is therefore referred to as 'physiological memory.' We developed a model of RF plasticity based on convergence in the auditory cortex of nucleus basalis cholinergic effects acting at muscarinic receptors, with lemniscal and nonlemniscal frequency information from the ventral and magnocellular divisions of the medial geniculate nucleus, respectively. In the model, the specificity of RF plasticity is dependent on Hebbian rules of covariance. This aspect was confirmed in vivo using microstimulation techniques. Further, the model predicts that pairing a tone with activation of the nucleus basalis is sufficient to induce RF plasticity similar to that obtained in behavioral learning. This prediction has been confirmed. Additional tests of the model are described. RF plasticity is thought to translate the acquired significance of sound into an increased frequency representation of behaviorally important stimuli.

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Introduction

Investigation of the neural basis of learning has traditionally ignored the role of neural plasticity in sensory cortices. This has occurred primarily for two reasons. First, the discovery of a 'critical period' limiting cortical plasticity to narrow time epochs during development of the visual and somatosensory cortices suggested that the potential for adult sensory cortex to express physiological plasticity was limited [Wiesel and Hubel, 1963, 1965; Van der Loos and Woolsey, 1973; Dawson and Killackey, 1987]. Second, the dominant assumptions of the investigators within the field included assertions that discharges of sensory cortex neurons had to remain stable (nonplastic) in order to maintain stable percepts of the external world, although ample evidence indicated that such 'stable' percepts were in fact actively recreated based upon information obtained during prior learning experiences [Boring, 1957; Gibson, 1969]. In this paper, we will review evidence that the receptive fields (RFs) of neurons in the primary auditory cortex (ACx) of adult animals are systematically altered by learning. We have identified a form of neural plasticity that is induced by associative learning and exhibits properties necessary for a putative neurobiological mechanism of memory formation. In particular, learning can quickly retune RFs of cells in the ACx of adult animals in a highly specific fashion, reflective of the information obtained during the behavioral training. We have called this form of neural plasticity 'CS-specific receptive field plasticity,' in reference to a cell's highly selective increased response to presentation of the frequency of the conditioned stimulus (CS) used to classically condition the animal. Based upon behavioral, physiological, pharmacological, and anatomical investigations of the ACx, we formulated a model of how three systems interact to induce and maintain CS-specific RF plasticity [Weinberger et al., 1990a, b]. This model contained predictions regarding the role of each system in generating and manifesting RF plasticity in ACx.

As will be detailed, this research effort has been a coordinated multilevel approach. Recordings of neuronal activity in a variety of cortical and subcortical areas during different learning paradigms (classical conditioning, instrumental conditioning, sensitization, and habituation) were made to determine their respective contributions in generating RF plasticity. Also, pharmacological and/or neurophysiological manipulations were utilized in order to probe a variety of putative mechanisms that could account for RF plasticity. This paper will review the phenomenon of CS-specific RF plasticity, summarize the mechanistic model, and describe recent results that confirm several aspects of the model. We will first cover the logic, assumptions, and background that form the foundation for the multilevel integrative approach used in this research endeavor.

RFs and Learning, a New Synthesis

Traditional interpretations of classical conditioning (Pavlovian or fear conditioning) concluded that animals learn the particular responses required to minimize the aversiveness of the reinforcing stimulus (the unconditioned stimulus, US). Thus, rabbits learn to extend their nictitating membrane in response to presentation of a tone that signifies the impending presentation of an airpuff to the eye. Learning to activate these highly refined muscle groups typically requires many trials, leading to the false impression that classical conditioning is a slow form of learning. However, it has been established that this view no longer best describes classical condi-

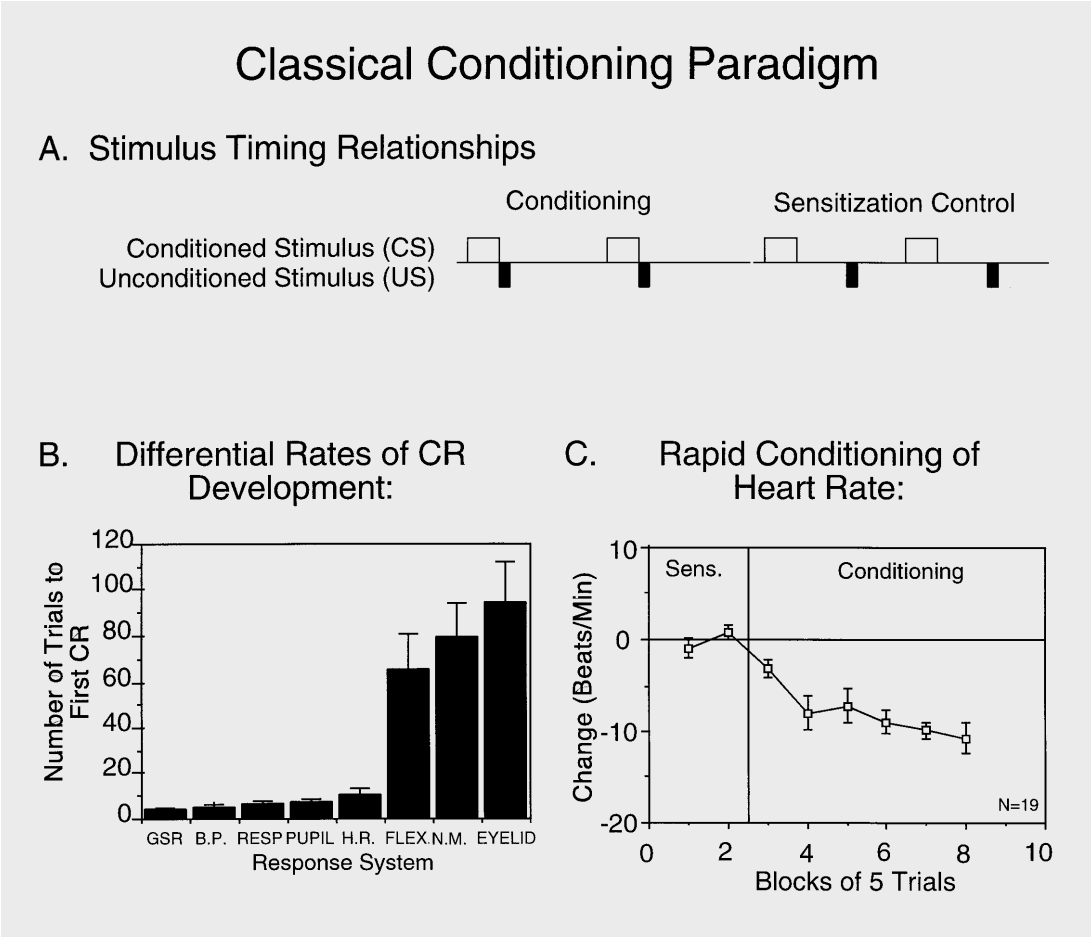

Fig. 1. A Timing relationships of the acoustic signal stimulus (white box) to be conditioned and the aversive US (black box) used in classical conditioning (left column) and sensitization control (right column) experiments. In classical conditioning, the CS reliably predicts the occurrence of the US. In sensitization, the relationship between the CS and the US is ambiguous. **B** Measurement of the development of conditioned responses (CRs) supports the two-stage theories of classical conditioning. Consistent conditioned responses emerge in nonspecific systems, such as heart rate, much earlier than in specific motor systems, such as the nictitating membrane response [Lennartz and Weinberger, 1992]. **C** Awake guinea pigs can develop conditioned bradycardia within the first block of five conditioning trials, indicating the rapid learning that can occur during classical conditioning [Edeline et al., 1993].

tioning [Mackintosh, 1983]. Contemporary learning theorists believe that classical conditioning produces learning in two stages [Rescorla, 1988]. During the initial training trials, the animal quickly learns the relationship between the signal stimulus (or CS) and the US (fig. 1A). During a subsequent second stage, the animal learns to act upon that association by manipulating appropriate muscle groups. This two-stage theory of learning is supported

by evidence showing that relatively few trials are required to develop consistent conditioned responses in nonspecific behavioral systems such as heart rate, and a much greater number of trials are required to develop conditioned responses in specific motor system responses, such as leg flexion or nictitating membrane (fig. 1B) [Lennartz and Weinberger, 1992, 1994]. We have selected classical conditioning as our model system of learning because of this ability of animals to learn the stimulus association rapidly, with the goal of detecting initial learning-induced changes in neural activity (fig. 1B, C).

Thus, we sought to identify changes in the coding and representation of the CS following behavioral training. However, it is essential that any changes in neuronal response patterns be specific to the learning situation, and not merely reflect alterations in stimulus intensity or nonspecific changes in arousal due to presentation of aversive stimuli. Previous investigations had demonstrated the development of increased responses (evoked potentials or neural discharges) in sensory cortex to the CS [for review, Weinberger et al., 1990a]. While prior investigators concluded that the increased responses were indeed due to learning, this interpretation was often compromised by lack of acoustic stimulus control (e.g., due to the use of freely moving subjects) or the absence of associative controls for sensitization (e.g. arousal state). Thus, we (1) investigated learning in a subject that would tolerate head restraint (the awake guinea pig), enabling constancy of acoustic intensity at the ear canal, and (2) incorporated sensitization controls to ensure that any potential neural correlates of learning were associative in nature.

However, these precautions alone are not sufficient to conclude that increased responses to the CS reflect the specific information provided by the CS. That is, the ultimate question of interest is 'Does learning specifically modify the processing of information about the CS?' Increased responses to the CS might either reflect a general increase in responsivity to all acoustic stimuli, or be largely limited to the CS itself (fig. 2). To distinguish between these two possibilities, recording responses to the CS alone is not sufficient. Rather, it is necessary to record the responses to many stimuli along the same stimulus dimension. By combining a traditional unit of sensory system physiology, the RF, with the major psychological model of learning, classical conditioning, it is possible to determine if the activity of ACx neurons is modified to specifically reflect information about the signal value of an acoustic stimulus. Thus, if learning led to an increase in response to all tonal frequencies, then even if this change in neural responsiveness were associative (i.e., sensitization groups did not develop this broadband increase), it would not reflect the specific information about the CS per se (fig. 2B).

However, if the cell's response to the frequency of the CS were increased, with little or no change to other, nontrained frequencies, then one could conclude that the neural plasticity did indeed reflect the specific nature of the training experience (fig. 2C). Thus, the power of RF analysis enables one to distinguish increases that appear quantitatively similar (hypothetically, both specific and nonspecific groups could develop increases at the frequency of the CS) from qualitatively different results (CS-specific RF plasticity vs. general increases in cellular responsivity).

Associatively Induced RF Plasticity in the Primary ACx

The first study on the effects of learning on RFs in a primary sensory cortex reported that classical conditioning produces a specific

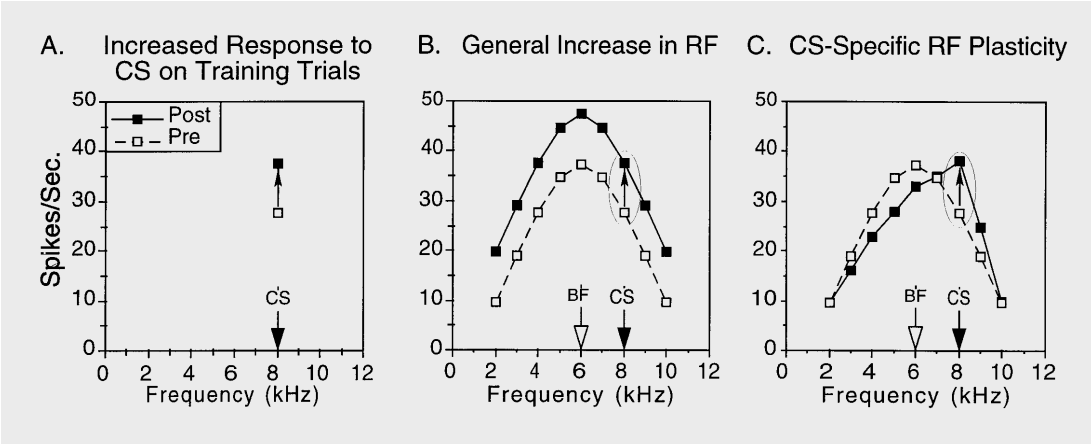

Fig. 2. A Conditioning has been reported to increase evoked neuronal responses, as illustrated in this example of hypothetical data. Following conditioning, the response to the CS frequency is greater (black square) than prior to the onset of learning (white square). This increase in response can occur in one of two ways. A general increase in responsivity across the cell's entire RF (**B**) or a highly specific increase to the frequency of the CS alone (**C**). The latter change in the RF might specifically reflect the information obtained during the learning situation. Measurement of the cell's entire RF before and after behavioral learning is necessary in order to distinguish between these quantitatively similar, but qualitatively different, response patterns [figure adapted from Weinberger, 1995b].

change rather than an increase in responsivity across the frequency RF [Bakin and Weinberger, 1990; see Diamond and Weinberger, 1986, for the first report that learning alters RFs in auditory cortical field AII). Adult guinea pigs, bearing microelectrodes that were chronically implanted in infragranular layers of primary ACx, were trained on a classical conditioning task by presenting a tone followed by a mild foot shock. The training was brief, consisting only of 10–30 pairings (trials) within a period of about 15–40 min. Behaviorally, subjects rapidly (5–10 trials) expressed typical signs of conditioned fear which persisted for the duration of training. RFs for frequency (i.e., 'tuning curves') were obtained prior to, immediately, 1 h, and 24 h after training [see Bakin and Weinberger, 1990; Edeline et al., 1993, for technical details regarding calibrated acoustic controls, recording methods, and behavioral measures]. The frequency of the CS was selected to be a frequency different from the best frequency (BF, the frequency to which neuronal response is greatest) in order to determine if classical conditioning shifts the tuning toward the frequency of the CS.

The results revealed that conditioning alters RFs in a highly specific manner. Responses to the frequency of the CS (and sometimes immediately adjacent frequencies) were increased, whereas responses to the BF were usually reduced; responses to other non-CS frequencies were often reduced if close to the BF. Responses to distant frequencies far from the CS frequency that generally exhibited weak or no response, i.e., were outside of the RF under study, did not change [Bakin and Weinberger, 1990]. The opposing changes between the CS frequency and the BF were often

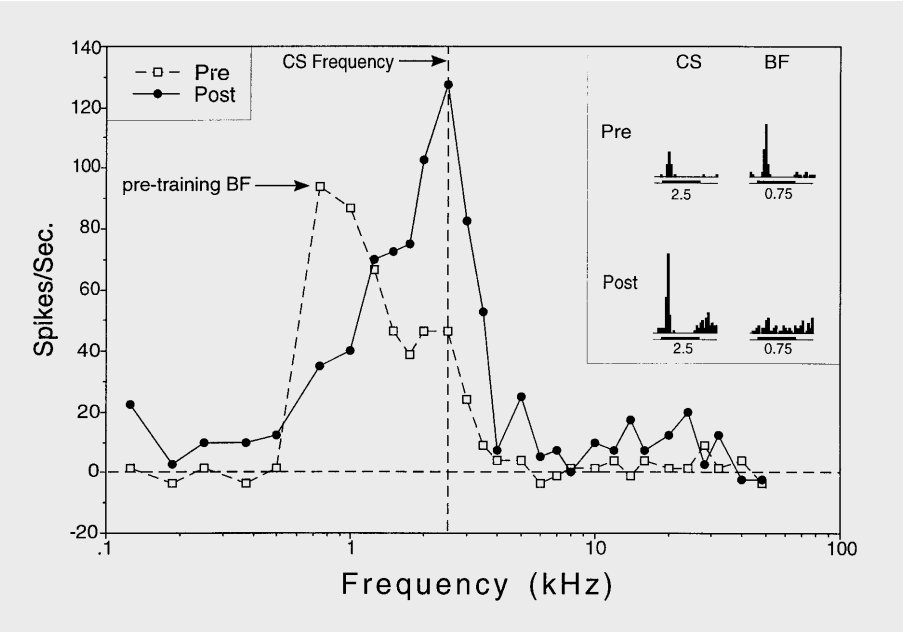

Fig. 3. CS-specific RF plasticity of a primary ACx single neuron. Prior to training, the BF of this cell was 0.75 kHz. Following classical conditioning with a CS of 2.5 kHz, the RF of this cell shifted such that the frequency of the CS became the cell's new BF. The inset shows the actual rasters and histograms of this change in the cell's response patterns for these two frequencies pre- and postconditioning [figure adapted from Weinberger, 1995b].

large enough to shift frequency tuning toward the frequency of the CS. In some cases, the shift was so large that the frequency of the CS became the new BF. Finally, the changes in tuning were very long-lasting, i.e., they were maintained at 24 h after training, the longest post-training interval tested in this first experiment (retention of CS-specific RF plasticity for many weeks is discussed below). Examples of CS-specific RF plasticity are provided in figures 3 and 4.

Following classical conditioning to a CS of 2.5 kHz, the BF of this cell's RF shifted to match the training stimulus (fig. 3). Note that these were not marginal responses. The inset documents the striking change in the response profile of this cell, as the pretraining BF evokes a minimal response post-training, but the response to the CS is greatly increased. In the example depicted in figure 4, a notch in a cell's RF was 'filled in' by learning (fig. 4A, B). Subtracting the pretraining quantified RF from the post-training RF (fig. 4C) reveals the actual effect of classical conditioning on the RF. The largest increase is to the frequency of the behaviorally relevant CS, responses decreased to other frequencies, including a maximal loss of responsiveness to the pretraining BF (fig. 4D).

This learning-induced RF plasticity is associative. Control subjects that received sensitization training (unpaired tone and shock) do

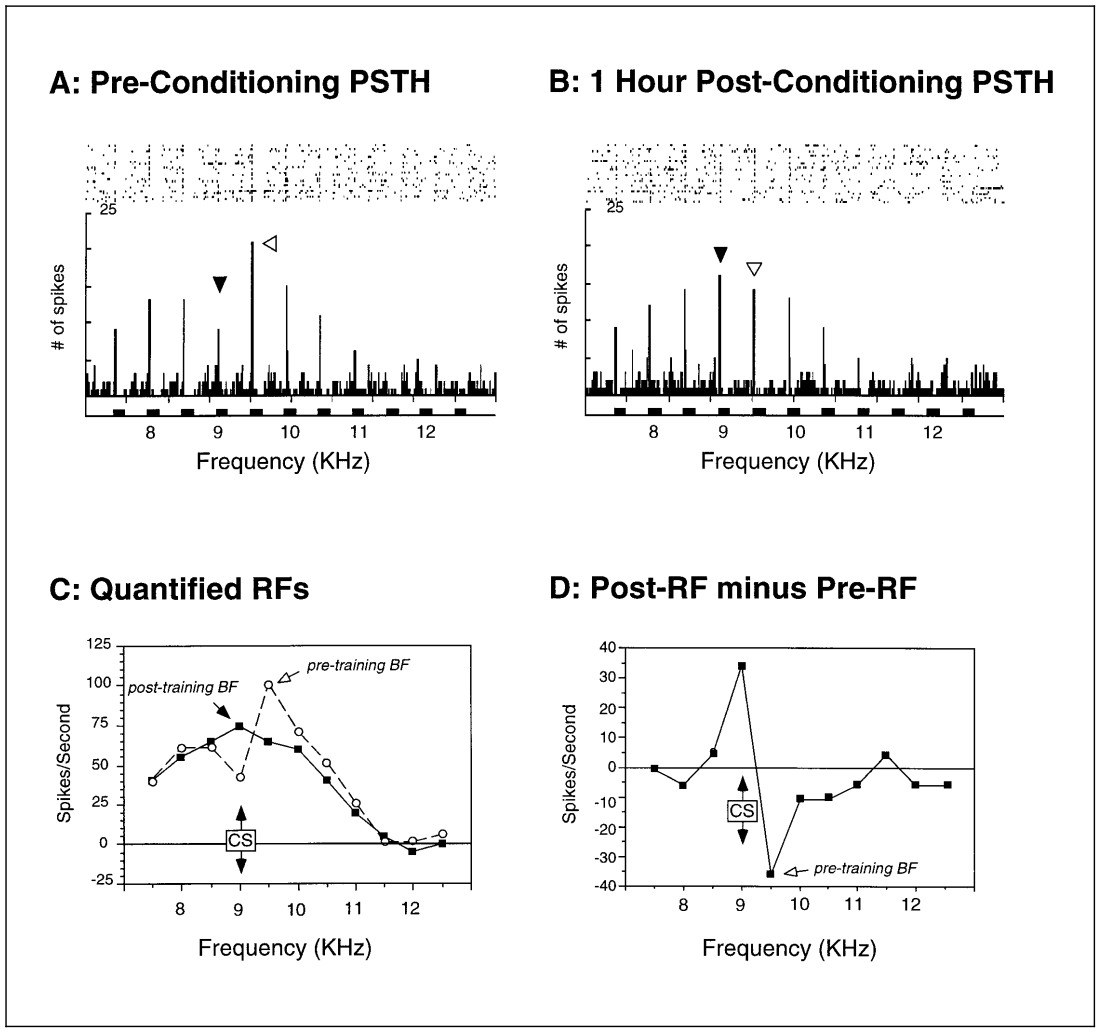

Fig. 4. CS-specific RF plasticity of a primary ACx single neuron. **A** Post-stimulus time histogram (PSTH) and raster obtained prior to classical conditioning. In this case, there was a 'notch' in the RF of this cell centered on 9.0 kHz. The pretraining BF of this cell was 9.5 kHz (white arrowhead). **B** Following classical conditioning with a CS of 9.0 kHz (black arrowhead), the RF of this cell shifted such that the frequency of the CS became the cell's new BF. **C** Quantification of the pretraining (dotted line) and posttraining (solid line) RFs shown in **A** and **B**. **D** Subtracting the pre-RF from the post-RF reveals that classical conditioning produced a highly specific change in the response profile of this cell, consisting of a maximal increase to the frequency of the CS, and a maximal decrease in response magnitude to the pretraining BF [figure adapted from Bakin and Weinberger, 1990].

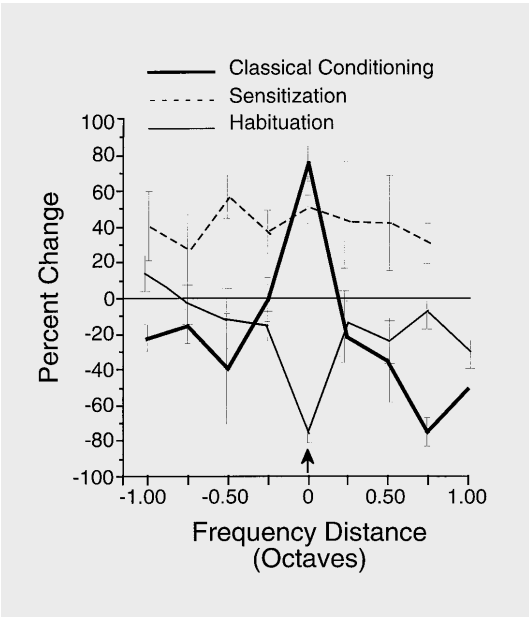

Fig. 5. Averages of RF difference functions for three different training paradigms underscore how learning produces modifications of RFs in adult ACx that reflect the acquired behavioral significance of the acoustic stimuli. As described previously, classical conditioning produces a highly specific increase in response magnitude to the frequency of the CS, with decreases or no change at other frequencies (heavy solid line). This CS-specific RF plasticity is associative, as animals given sensitization training develop general increases in response magnitude across the entire RF (dotted line), which parallels the increased sensitivity of these animals to any acoustic stimuli. Finally, habituation training, in which one acoustic stimulus is presented repeatedly without behavioral reinforcement produces a highly specific decrease in response magnitude to the repeated frequency (thin solid line). This RF plasticity parallels the accompanying specific decrease in the ability of that frequency to elicit a behavioral response from the animal [figure adapted from Bakin and Weinberger, 1990; Bakin et al., 1992; Condon and Weinberger, 1991].

not develop CS-specific RF plasticity. Rather, they developed a general increase in response to all frequencies (fig. 5). Moreover, this general increase in responsivity is not even modality-specific. Sensitization training in which subjects receive a visual stimulus (flashing light) and shock randomly also develop a general increase in their auditory frequency RFs [Bakin et al., 1992]. Finally, habituation training, in which an acoustic stimulus is presented repeatedly without reinforcement, and thereby loses its ability to evoke a behavioral response from an animal, produces a decrement in the RF that is specific to that stimulus [Condon and Weinberger, 1991]. Subsequent studies have shown that RF plasticity develops rapidly, within the first five trials [Edeline et al., 1993]. Furthermore, RF plasticity lasts indefinitely, as tested at retention intervals as long as 8 weeks [Weinberger et al., 1993]. Moreover it is highly robust across brain states. Thus, RF plasticity that is induced in waking, behaving animals is expressed subsequently while they are under general anesthesia [Weinberger et al., 1993].

This last finding also is pertinent to an obvious problem. It might be thought that presentation of the frequency of the CS during post-training RF determination produces arousal, and that increased responses to the CS frequency are therefore attributable to this increased arousal. However, putative CS-evoked arousal cannot occur in subjects under deep barbiturate anesthesia, yet RF plasticity induced in the waking state can be expressed under deep general anesthesia [Weinberger et al., 1993]. There are also other grounds to rule out putative arousal. First, the latency of cortical EEG arousal is longer than the latency of the evoked tuned discharges in the ACx [Diamond and Weinberger, 1989]. Second, it does not explain decreased responses to non-CS frequencies. Third, direct measures of arousal reveal no such changes during RF determination [Weinberger and Lindsley, 1964].

In summary, classical conditioning using a tonal conditioned stimulus produces CS-specific changes in frequency RFs in the ACx. Responses to the CS frequency are increased, while responses to the pretraining BF, and many other frequencies, are decreased. This learning-induced RF plasticity is associative; sensitization training produces only general increased responses across RFs. Further, RF plasticity is highly specific to the frequency of the CS, with adjacent frequencies only a small fraction of an octave from the CS frequency not eliciting increased responses. Additionally, RF plasticity develops extremely rapidly, being evident after only five training trials, the fewest tested. Finally, it is enduring, lasting 8 weeks, the longest retention interval examined. Overall, these characteristics are essentially the same as those of some forms of associative memory (e.g., priming or declarative, as opposed to procedural or skill memory which do not develop as rapidly) [Schacter and Tulving, 1994]. We turn now to a model of how this RF plasticity is induced by associative conditioning.

The Model

Components of the Model

The model is based on the convergence of three subcortical systems at the primary ACx: (1) auditory lemniscal, (2) auditory nonlemniscal, and (3) cholinergic neuromodulatory. To provide the rationale for the model, we now review the salient characteristics of these systems. As we have emphasized elsewhere [Weinberger et al., 1990a, b], the model is preliminary in the sense that it provides only an overall architecture of a two-stage process that we believe leads to RF plasticity in the primary ACx. However, it does not include every brain structure that might be involved in some way (e.g., the hippocampus) nor does it present detailed hypotheses regarding intracortical processes such as lateral inhibition, recurrent inhibitory networks, intralaminar interactions, etc.

Auditory Lemniscal: The Ventral Medial Geniculate Body (MGv). The primary ACx is organized in a tonotopic manner, i.e., the representation of sound frequencies is topographically isomorphic with the functional organization of the basilar membrane. The subcortical lemniscal auditory system maintains a topographic 'map' of frequency from the cochlea through its successively higher levels. The MGv projects to layer IV of the primary ACx in a topographic manner, thus providing the basis for the systematic map of frequency at the cortex. Neurons of the MGv respond only to acoustic stimulation and are narrowly tuned to acoustic frequency [reviewed in Aitkin, 1990]. Of particular relevance, MGv cells are unchanged by learning [Gabriel et al., 1975; Ryugo and Weinberger, 1978; Birt and Olds, 1981; Edeline et al., 1988; Edeline and Weinberger, 1992]. Furthermore, MGv cells either do not develop RF plasticity or exhibit only transient plasticity of less than 1 h [Edeline and Weinberger, 1991]. Thus, long-term retention of RF plasticity in the ACx cannot be accounted for by 'projected' plasticity from the MGv.

Auditory Nonlemniscal: The Magnocellular Medial Geniculate Body (MGm). The auditory thalamus also includes a nonlemniscal component, the MGm, whose characteristics are generally opposite to those of the lemniscal MGv. The MGm has no systematic map of sound frequency, its neurons project to the primary ACx (as well as to all other auditory cortical fields) in a widespread diffuse manner rather than topographically and they terminate primarily in layers I, II, and VI, avoiding layer IV [Herkenham et al., 1986; Winer, 1992]. Moreover, the MGm responds both to acoustic and to somatosensory, particularly

noxious, sensory stimulation [Wepsic, 1966; Love and Scott, 1969]. In contrast to the MGv, the MGm is greatly affected by learning. Its neurons develop learning-induced increased responses to acoustic CS during classical conditioning trials, including differential neuronal plasticity during discrimination training to two acoustic stimuli [Gabriel et al., 1975; Ryugo and Weinberger, 1978; Birt and Olds, 1981; Weinberger, 1982; Edeline et al., 1988; Edeline and Weinberger, 1992]. Furthermore, they develop specific, long-lasting RF plasticity [Edeline and Weinberger, 1992].

Cholinergic Neuromodulatory: The Nucleus basalis (NB). The third component of the model is the NB. The major subcortical source of cortical acetylcholine (ACh) [Johnston et al., 1979, 1981; Lehman et al., 1980; Hartgraves et al., 1982; Weinberger, 1982; Mesulam et al., 1983], the NB has long been known to be critically involved in learning situations that appear to be cortically dependent. For example, blockade of the central cholinergic system impairs learning in animals and humans [Deutsch, 1971; McGaugh, 1989]. Further, NB-elicited release of ACh in the cerebral cortex is necessary to shift the EEG from the synchronized (high voltage slow waves) to the desynchronized (low voltage fast waves) pattern that characterizes the waking state [McKenna et al., 1989; Buzsaki and Gage, 1991; Metherate et al., 1992] and is likely to be optimal for much learning and behavioral function. For explication of the model, we confine our consideration to its hypothesized effects on primary ACx.

Cholinergic agonists (ACh or the specific muscarinic agonist acetyl-beta-methacholine) applied to neurons in primary ACx of the waking cat produce atropine-sensitive frequency specific changes in RFs, including tuning shifts with decreased response to the BF and increased responses to an adjacent frequency [McKenna et al., 1989]. Further, endogenous ACh can produce tuning changes in the ACx as iontophoresis or micropressure application of anticholinesterases produces tuning shifts which were similar to those obtained with muscarinic agonists [Ashe et al., 1989]. Overall, the observations indicate that endogenous ACh, acting at muscarinic receptors, can produce organized modification of RFs. However, these changes in tuning when tones are given in the presence of cholinergic agents might only reflect the potential for RFs to change during alterations in behavioral state. Pairing a tone with iontophoretic application of muscarinic agonists produces changes in the frequency RF that are specific to the frequency of the paired tone; this effect can be blocked by atropine [Metherate and Weinberger, 1989, 1990]. Thus, activation of the cholinergic system can modulate RF tuning either in an associative manner or as a potential response to a shift in behavioral state. Finally, there is evidence of involvement of the NB in learning. Cells in the NB are sensitive to motivational state and change their discharges to sensory input during learning [Burton et al., 1976; Mora et al., 1976; Rolls et al., 1979; Richardson and DeLong, 1986].

Operation of the Model

In this section, we will review the hypothesized operation of the model constructed to explain CS-specific plasticity of frequency RFs in primary ACx. We hypothesized [Weinberger et al., 1990a, b] that the (a) auditory lemniscal nonplastic input from the MGv, (b) the auditory nonlemniscal plastic input from the MGm and (c) the neuromodulatory muscarinic cholinergic input from the NB act synergistically during learning. The model is summarized in figure 6.

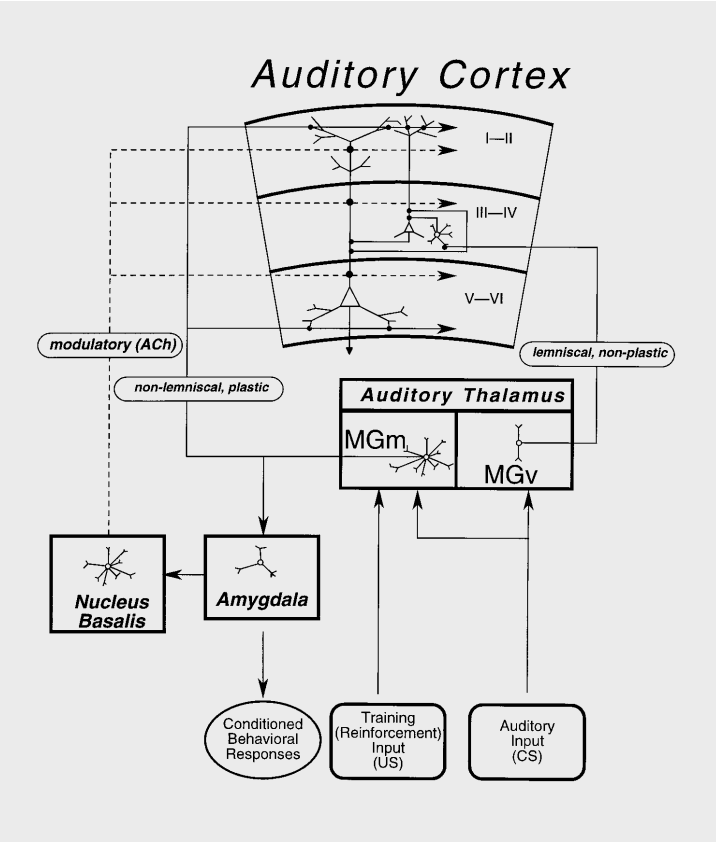

Fig. 6. Schematic model of the anatomical projections of the three systems that act synergistically within the ACx to produce and maintain CS-specific RF plasticity and conditioned behavior. Together, the three systems (1) provide detailed frequency information to the ACx (via the lemniscal nonplastic pathway originating in the MGv), (2) indicate the behavioral significance of the acoustic stimulus (via the nonlemniscal plastic pathway originating in the MGm), and (3) produce neuromodulation proportional to the importance of the auditory stimulus (by the modulatory cholinergic projection originating in the NB). In brief, auditory and nonauditory inputs converge in auditory thalamus. Learning produces increased responses in the MGm, which are projected to the NB and the ACx. Increased NB activity produces increased cholinergic release in the ACx, which combined with increased synaptic drive from the auditory thalamus, produces long-lasting plasticity in the ACx [see text for details; figure adapted from Weinberger et al., 1990a, b].

In addition, two modified Hebbian rules [Hebb, 1949; Stent, 1973] were invoked to explain increased responses to the CS frequency and decreased responses to non-CS frequencies: (I) If a presynaptic input and the postsynaptic cell are both active at the same time, then synaptic strength is increased. (II) If the presynaptic input is not active but the postsynaptic cell is active, then synaptic strength is weakened. 'Active' refers to a state of increased excitability and is not restricted to cellular discharges. Of course, all behavioral and neural theories of sequential associative learning (e.g., classical conditioning) assume that the CS leaves a 'neural trace' that persists in some form long enough to still be present at the time that a subsequent reinforcer (the US in classical conditioning) occurs, presumably a prerequisite for neural 'association'. This trace need not consist of neuronal discharges but more likely involves cellular processes that outlast spike production. Thus, associative hypotheses, like the present model, do not require strict coincidence of neural discharges. Until 'neural traces' are understood and integrated into testable models, all such models will be incomplete. Our preliminary model does not include a precise or detailed exposition of Hebbian rules, which have several slightly different formulations. For the purposes of this paper, the covariant nature, or lack thereof, of pre- and postsynap-

tic states is adequate, withoutfurther consideration of the detailed levels or changes of level of these activity states.

We added a corollary to the Hebbian rules: (C1) The amount of change in synaptic strength is proportional to the degree of postsynaptic excitability. Thus, the greater the postsynaptic excitability, the greater the increased strength (rule I) or decreased strength (rule II). During CS-US pairing trials, the MGv provides unaltered, detailed frequency input to layer IV which rapidly engages pyramidal cells in the infragranular layers V and VI (pyramidal cells in layer III may also be involved but RF studies in learning have not yet been accomplished for supragranular layers). In contrast, the MGm, which receives both CS and US input, is thought to be the first site of associative plasticity. Although it can develop differential frequency-specific changes to a CS+ (the tone that predicts the US) vs a CS– (a tone stimulus not paired with, and therefore not predictive of, the US) during discrimination training, cells in this nucleus exhibit extremely broad and complex tuning, quite unlike the lemniscal auditory system or the ACx. Therefore these cells can provide little if any detailed frequency information to the ACx. But the MGm can project an increased response to the CS to the apical dendrites in layers I–II (perhaps also to basal dendrite of pyramidal cells whose soma are in layers V/VI). In short, the MGm can 'signal' the forthcoming US by increasing the depolarization of apical dendrites when the CS is presented on a training trial. However, the MGm depolarization of the apical dendrites is weak at the soma, due to the decremental character of excitatory postsynaptic potentials and the short length constant from the synaptic sites in layers I/II to the cell bodies. Therefore, although the convergent MGv and MGm excitatory inputs satisfy Hebbian rule I, the effect is weak (see corollary C1) and is expected to not be long-lasting by itself.

However, the MGm also engages the cholinergic NB system. It is hypothesized to do so indirectly, by providing increased input to the lateral nucleus of the amygdala, thence to the central nucleus of the amygdala which in turn projects to the NB (this conditioned neuronal response of the MGm was hypothesized to initiate many emotional and behavioral responses by activating the amygdala). The result would be an increased release of ACh within the ACx. The release of ACh in the ACx is hypothesized to amplify the input from the MGm onto the apical dendrites of pyramidal cells. In short, the NB is thought to produce a widespread enhancement of postsynaptic activation during training trials.

Application of the Hebbian rules explains the strengthening of responses to the CS as follows. During training trials, the synapses carrying CS information from the MGv are strengthened because (1) they have presynaptic activity and (2) increased postsynaptic activity [caused by depolarization from the MGm onto the apical dendrites of cortical pyramidal cells (rule I) and amplification of this depolarization by ACh acting at muscarinic receptors (corollary C1)]. Synapses for non-CS frequencies in the ACx are thought to be weakened, as follows. During training trials, non-CS inputs to the ACx (and also to the MGm) are inactive because only the CS frequency is presented during CS $\rightarrow$ US paired conditioning trials. Nonetheless, postsynaptic pyramidal cells in the ACx are excited by the MGm and NB influences, as explained above. This 'mismatch' results in a decrease in synaptic strength for non-CS frequency synapses (rule II). The overall result is seen in post-training cortical RFs as increased responses to the CS frequency and decreased responses to many non-CS frequencies. If the opposing changes are large enough, then fre-

quency tuning will be shifted toward or to the frequency of the CS. In summary, the model hypothesizes that synapses are first changed in the MGm and next changed in the synapses between layer IV cells, which receive frequency-specific input from the MGv, and layer V and VI cortical pyramidal cells. The cholinergic input is thought to modulate the amount of synaptic change rather than be essential for such changes. Thus, the MGm input itself may produce plasticity but the strength and therefore the duration of the plasticity depends upon the NB muscarinic effect on the cortex. While the general processes proposed above are thought to be operative, there are several caveats. None are fatal to the model, but all need to be noted and ultimately resolved.

First is the issue of sequential temporal engagement of the components of the model. As pointed out above, the common assumption of the neural trace of the CS means that although the MGm is excited at a longer latency than the MGv, its cortical effects can still interact with the response of the cortex to the CS. The same holds for the subsequent activation of the NB and release of ACh in the cortex.

Second, a related issue is that activation of the NB preceding the CS would seem to satisfy the conditions for RF plasticity. And indeed prior stimulation of the NB does produce muscarinically mediated facilitation of sensory responses [Ashe et al., 1989; McKenna et al., 1989]. However, cortical cells are in a different state when excited by an acoustic stimulus prior to engagement of muscarinic receptors; they are depolarized, i.e., the NMDA channel is open. Therefore post-tone engagement of muscarinic receptors can be expected to have different effects than pretone engagement. The exact nature of these differences, which may be critical for associative neural plasticity, is under study [reviewed in Weinberger and Ashe, submitted] and will be critical for the current model.

Third is the issue of 'afferent specificity'. Findings show that increased response to the CS frequency is accompanied by decreased response to other (non-CS) tones including those that are only a fraction of an octave distant. Following current understanding of neuronal function, if a given synapse is strengthened, then such strengthening applies to all frequency information that is transmitted by that synapse, and vice versa for synaptic weakening. Therefore, if a synapse transmits information about both the CS frequency and also one or more non-CS frequencies, then strengthening would increase responses to both types, and similarly, weakening would decrease responses to both CS and non-CS frequencies. Thus, there would be no selective increased response to CS vs. non-CS frequencies.

This logic is straightforward, but it applies only to synapses that are involved in processing both CS and non-CS information. Because of the specific tuning of various MGv neurons, there will be neurons which do not carry CS information. The synapses of these cells may be called, colloquially, 'non-CS' synapses. They could be weakened without affecting synaptic responses to the CS frequency. This leaves the problem of synapses that carry both CS and non-CS information. As pointed out above, if such synapses are strengthened during training trials, then they would exhibit facilitation to non-CS frequencies. However, this would be restricted to non-CS frequencies within the relatively narrow domain of tuning of these MGv cells. A CS-specific change in tuning in the primary ACx might still result from synaptic weakening to non-CS frequencies and strengthening of synapses that carry both CS and non-CS information. This would depend upon the net effects of both types of change. To investigate this possibility, we

have conducted computer simulations of this situation. The results confirm the possibility that the hypothesized changes in synaptic strength of inputs from MGv cells could produce CS-specific RF plasticity, including shifts in tuning [Weinberger and Ashe, submitted]. A similar but more elaborate computational model of Armony et al. [1995] also produces the RF findings that we have reported. Therefore, although not intuitively obvious, simulations suggest that the type of formulation advanced here could account for some aspects of RF plasticity. However, appropriate physiological studies need to be performed.

Another issue concerns decreased responses to frequencies 'near' the CS frequency but no change to 'distant' frequencies, often those lying outside the RF of the cell in question. Modified Hebbian rule II cannot account for the lack of change of distant frequencies because these cases also satisfy this rule for synaptic weakening, i.e., no presynaptic activation with postsynaptic activation. However, as such distant frequencies generally had no response, the lack of a decrease (from no response to inhibitory response) might be attributable to synaptic weakening insufficient to be revealed as actual suppression. If this should prove not to be the case, then Hebbian rule II would be insufficient and perhaps non-Hebbian mechanisms (e.g., lateral inhibitory processes within the cortex) might be critical. For example, sideband inhibition that decreases in strength as a function of frequency distance from the CS frequency might account both for reduced responses near the CS frequency and no change in response to distant frequencies. In fact, having reviewed both the logical requirements to substantiate Hebbian formulations and evidence in favor of Hebbian processes in the cortex, we have found less positive evidence than might be supposed and have urged that undue emphasis should not be placed on Hebbian rules, particularly to the exclusion of alternative approaches [Cruikshank and Weinberger, 1996a].

Empirical Support for the Model

The model has been supported by studies of the medial geniculate nucleus, the NB and the ACx. A detailed review has been provided elsewhere [Weinberger and Ashe, submitted]. Here we provide a brief summary of this evidence.

Medial Geniculate

At the level of the auditory thalamus, the model states that convergence of CS and US information first takes place in the MGm and the results of this plasticity are then conveyed to other structures, specifically to the amygdala, NB and ACx. Therefore, plasticity should be evident in the MGm first. McEchron et al. [1995] recorded simultaneously in the MGm and amygdaloid central nucleus during discriminative (two-tone) classical conditioning and obtained shorter latency plasticity in the MGm than in the amygdaloid central nucleus, supporting the model.

The model asserts that learning produces synaptic plasticity in the MGm, specifically that synapses carrying acoustic (CS) input are strengthened by classical conditioning. This feature of the model was based on findings of associative plasticity in the MGm during classical conditioning (reviewed above). However, there had been no direct test of this claim. Recently, McEchron et al. [1996] studied monosynaptic single-cell discharges in the MGm, elicited by stimulating its auditory input, the brachium of the inferior colliculus, or input from another modality originating in the superior colliculus. Following conditioning to a tone, they found facilitation of re-

sponses specifically to the acoustic input from the brachium of the inferior colliculus but no change in response to test stimuli of the non-acoustic input from the superior colliculus. These findings support the model by indicating that classical conditioning appears to produce acoustic-specific synaptic facilitation in the MGm.

The model holds that synaptic strength for a tone should be facilitated if it is immediately followed by strong activation of the MGm, as would happen if a tonal CS were followed by an increased response of the MGm to the CS, based on associative plasticity in this nucleus. This would satisfy modified Hebbian rule I, that is both presynaptic (MGv response to the CS) and postsynaptic activation (MGm depolarization of cortical cells). Moreover, this facilitation should be maintained for minutes or hours rather than being transient, because MGm activation would result in activation of the NB (via the amygdala), releasing ACh in ACx. Weinberger et al. [1995] observed such long-term heterosynaptic facilitation when a tone was followed by stimulation of the MGm, supporting the model.

Nucleus Basalis

The model hypothesizes that the NB promotes long-lasting RF plasticity in the ACx, specifically by releasing ACh in response to the CS during training trials. If NB activation to a CS is causal to plasticity in the ACx, then neurons in the NB should develop enhanced responses to the CS and should do before cells in the ACx exhibit learning-dependent effects. This was recently reported by Maho et al. [1995].

If the model is valid, then substituting stimulation of the NB for the peripheral shock US should induce RF plasticity in the ACx. Moreover, this effect should be mediated by muscarinic receptors in the ACx. In order to directly test the role of the cholinergic system in inducing ACx RF plasticity, we stimulated the NB following acoustic stimulus presentation using timing constraints determined by behavioral conditioning [Bakin and Weinberger, 1996; unpublished observations]. Previous experiments investigating the effects of pairing NB stimulation or ACh modification of ACx RFs typically used stimulus presentation schedules that do not support behavioral conditioning, such as stimulating the NB prior to delivery of the signal cue. If, as we hypothesized, increased NB activation results during classical conditioning, then it is necessary to show that these cholinergic-induced RF modifications can be induced by stimulus presentation schedules typical of behavioral conditioning. Thus, following characterization of an ACx RF, animals were presented with a single tone followed by microstimulation of the NB (40 paired trials, total). Post-pairing RFs were measured and compared to those obtained prior to pairing (fig. 7A).

Using this protocol, ACx RFs developed CS-specific RF plasticity similar to that observed in animals that underwent behavioral training. Following 40 paired presentations of a 4.0-kHz tone with NB stimulation, this cell developed a stronger response to 4.0 kHz, and weaker responses to adjacent frequencies, including the pre-pairing BF (fig. 7B, C). This observation is identical to RF changes observed in animals that underwent behavioral training. This CS-specific modification of the RF was stable, as indicated by the consistent shape of the post-training RF tuning curve obtained 20 min following the cessation of the pairing procedure (fig. 7D). The largest increase in response was at the paired frequency (fig. 7E, closed arrowhead), and decreases were observed at other frequencies, including the pretraining BF (fig. 7E, open arrowhead).

Paired tone/NB stimulation produced CS-specific modification in RFs that was similar across subjects. The group difference function

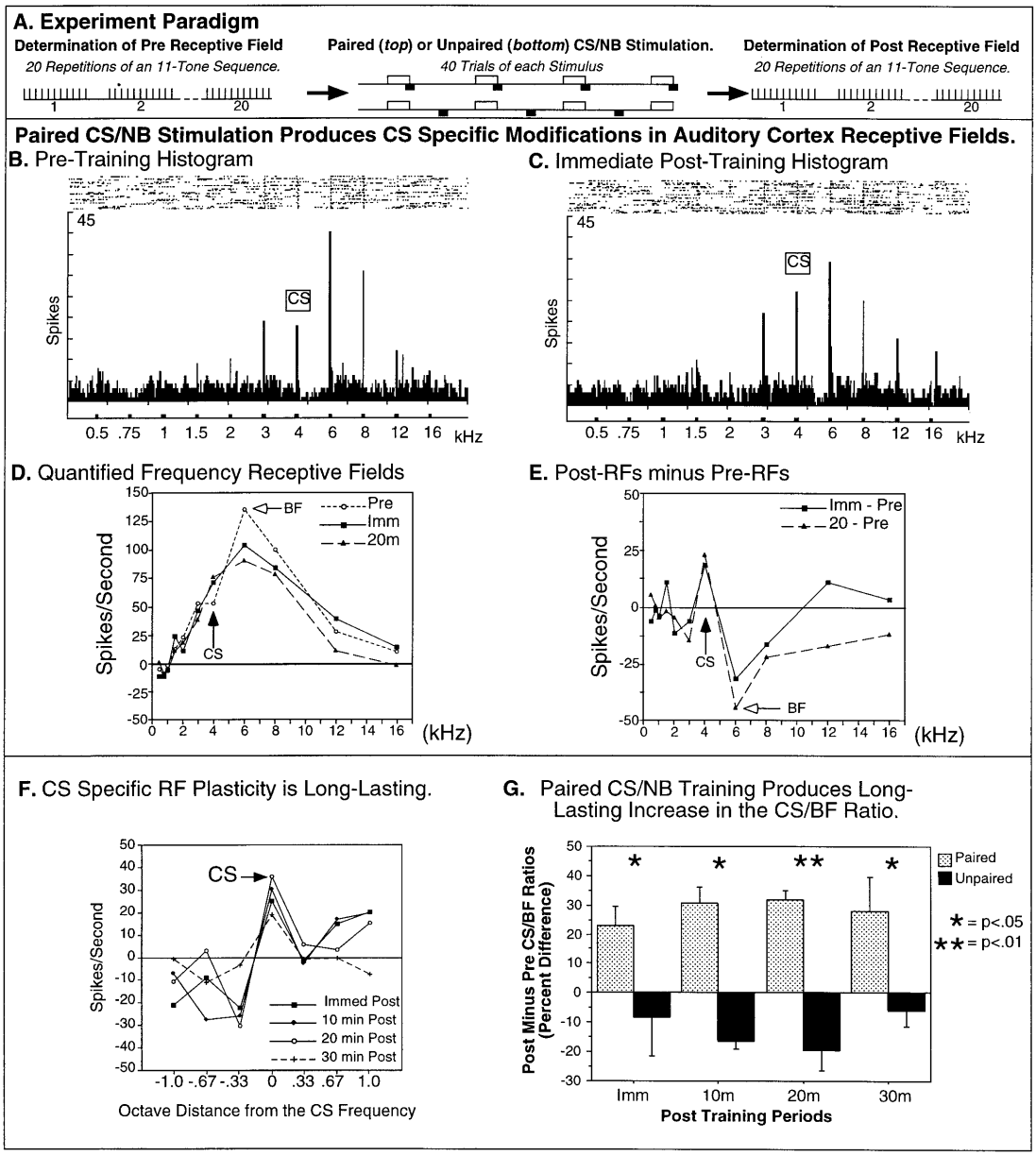

Fig. 7. The role of the NB in inducing and maintaining CS-specific RF plasticity. **A** Schematic illustrating the testing protocol used in this experiment. After an initial assessment of a cell's RF, the subject was given either 40 paired or unpaired trials of CS+/NB microstimulation. Immediately following the last pairing trial, the cell's RF was recharacterized. Subsequent retention tests occurred at 10-min intervals. **B** Prior to pairing, this cell's RF responded to a narrow range of frequencies. The BF was 6.0 kHz. **C** 4.0 kHz was selected to be the CS. Immediately following the pairing procedure, this cell's response to 4.0 kHz increased. **D** Quantification of the post-stimulus time histograms demonstrates the increase in response to the CS+ and the decrease in response to the pretraining BF (pretraining RF: solid line; post-training RFs: dot-

illustrates that the average effect of pairing a tone with NB stimulation is stable up to 30 min post-pairing (fig. 7F). The pairing procedure produced a long-lasting increase in the CS/BF ratio, a measure of the magnitude of the responses to the CS and the BF, indicating that following pairing of the CS with NB stimulation, the cell responds greater to the CS relative to the BF than it did prior to training (fig. 7G). Finally, animals that received unpaired presentations of tones and NB stimulation did not develop CS-specific RF plasticity (fig. 7G), indicating that this NB stimulation-induced plasticity is also associative, similar to behaviorally trained animals. Thus, pairing tone presentation with NB stimulation using timing relationships similar to those used in behavioral training is sufficient to induce CS-specific RF plasticity similar to that observed in behaviorally trained animals.

These findings were obtained in urethane-anesthetized adult guinea pigs, thus excluding any potential for arousal-induced changes in RF. However, if the model applies to the normal behavior of awake subjects, then it is necessary to establish NB induction of RF plasticity in the waking state. This has recently been confirmed [unpublished observations]. Further, NB-induced RF plasticity is retained for up to 24 h postpairing, the longest interval yet tested, indicating long-term retention of NB-induced RF plasticity. A critical finding of this investigation was that RF plasticity only developed in subjects whose NB stimulation was effective in producing EEG desynchronization. EEG desynchronization can also be used to determine if the effects of NB stimulation were mediated by muscarinic receptors, as hypothesized by the model. Systemic or direct cortical application of atropine blocked the NB stimulation-induced EEG desynchrony, indicating that this effect was indeed mediated by muscarinic receptors. Thus, we believe that this aspect of the model, namely the role of the NB in inducing CS-specific RF plasticity following behavioral training, has been confirmed.

Auditory Cortex

The role of Hebbian rules in the induction of ACx RF plasticity was directly evaluated by systematically varying the pre- and postsynaptic activation levels of single cells in urethane-anesthetized guinea pigs [Cruikshank and Weinberger, 1996b]. Presynaptic activation was controlled by selection of tone frequency. The RF of a cell characterizes the ability of tones to activate the postsynaptic cell afferents. Selection of a CS and a CS– (a tone stimulus not paired with, and therefore not predictive of, the US) based upon the cell's RF can therefore select different populations of afferent inputs. Presentation of one frequency would then result in the activation

ted lines). **E** Subtracting the pretraining RFs from the post-training RF reveals the CS-specific nature of the RF plasticity induced by paired tone/NB stimulation. Immediately following pairing (solid line), the biggest increase was at the frequency of the CS (black arrowhead) and the biggest decrease was at the frequency of the pretraining BF (white arrowhead). This modification of RF tuning was maintained for up to 20 min (dotted line). **F** Group difference functions reveal that across all animals, pairing of a CS with NB stimulation produced a CS-specific increase in the RF (black arrowhead). This increase was maintained. **G** The CS/BF ratio is a measure of the response of the CS relative to the pretraining BF. Pairing a CS with NB stimulation produced a long-lasting significant increase in the CS/BF ratio, indicating a stronger response to the CS with respect to the BF following training. Further, this plasticity was associative, as subjects receiving unpaired presentations of tones and NB stimulation did not produce any change in the CS/BF ratio [figure adapted from Bakin and Weinberger, 1996].

of the afferent population sensitive to that frequency, and the lack of activation of afferents that do not respond to that frequency, enabling independent control of different presynaptic populations.

Control of postsynaptic activation levels was obtained by applying minimal depolarizing or hyperpolarizing current pulses from a juxtacellular electrode. Effective control of postsynaptic activity levels is illustrated by the increased cellular discharges during application of depolarizing current (fig. 8, left column, rows 2 and 4) and the complete cessation of cellular discharges during application of hyperpolarizing current (fig. 8, right column, rows 2 and 4).

With independent control of both presynaptic and postsynaptic activation levels of a single ACx neuron, it was possible to directly determine if induction of RF plasticity follows the modified Hebb rules previously described. Thus, this experiment predicted that pairing of increased afferent activity (tone presentation) and increased postsynaptic activity (depolarizing current) should result in increased responses to the tone, as would be expected if the synaptic strength between the afferents activated by the tone and the postsynaptic cell was increased. The covariance component of the Hebbian hypothesis was tested by producing a mismatch in activation levels between the presynaptic afferents and the postsynaptic cell by pairing increased presynaptic activity (tone presentation) with decreased postsynaptic activation (hyperpolarizing current). Thus, if this hypothesis is true, cortical cells should respond less to a tone following paired presentations of that tone with hyperpolarizing current.

Results from this experiment are depicted in figure 8. Prior to pairing the RF of this cell was determined and two frequencies were selected to be the CS+ (paired with footshock) and the CS– (no shock presented). The CS– initially evoked a greater response from this neuron than the CS+ (fig. 8, row 1). After assessment of the stability of this cell's responses, the CS+ was presented concurrently (paired) with depolarizing current and the CS– was paired with hyperpolarizing current (60 trials, fig. 8, row 2). Immediately following this initial pairing procedure, the cell's response to the CS+ increased, and the response to the CS– decreased (fig. 8, row 3, left and right column, respectively). This effect was more pronounced following an additional 60 trials of pairing (fig. 8, rows 4 and 5). Thus, induction of RF plasticity in this neuron appeared to be determined by Hebbian rules. Of note, this plasticity was more likely to occur if the overall state of ACx was aroused as indicated by a desynchronized EEG. This is consistent with the findings mentioned earlier, namely, that NB stimulation induction of RF plasticity only occurs in subjects whose NB–stimulating electrodes could desynchronize the EEG at the time of tone/NB stimulation pairing. Approximately 32% of ACx neurons tested in this fashion developed RF plasticity consistent with the Hebb hypothesis, in contrast to only 5% that developed RF plasticity in the opposite direction, a statistically significant difference. This experiment demonstrated that Hebb rules can govern sensory cortical plasticity in the adult, and confirmed this aspect of the model: namely Hebbian induction of ACx RF plasticity.

Finally, in the original 1990 description of the mechanism of RF plasticity, we considered what the effect of learning would be upon the spatial representation of frequency within the ACx [Weinberger et al., 1990a, b]. Because ACx neurons are organized into a frequency map, we predicted that if learning produces shifts in the tuning of ACx neurons to or towards the frequency of the training stimulus, resulting in more neurons having BFs equal to that of the training stimulus, then the

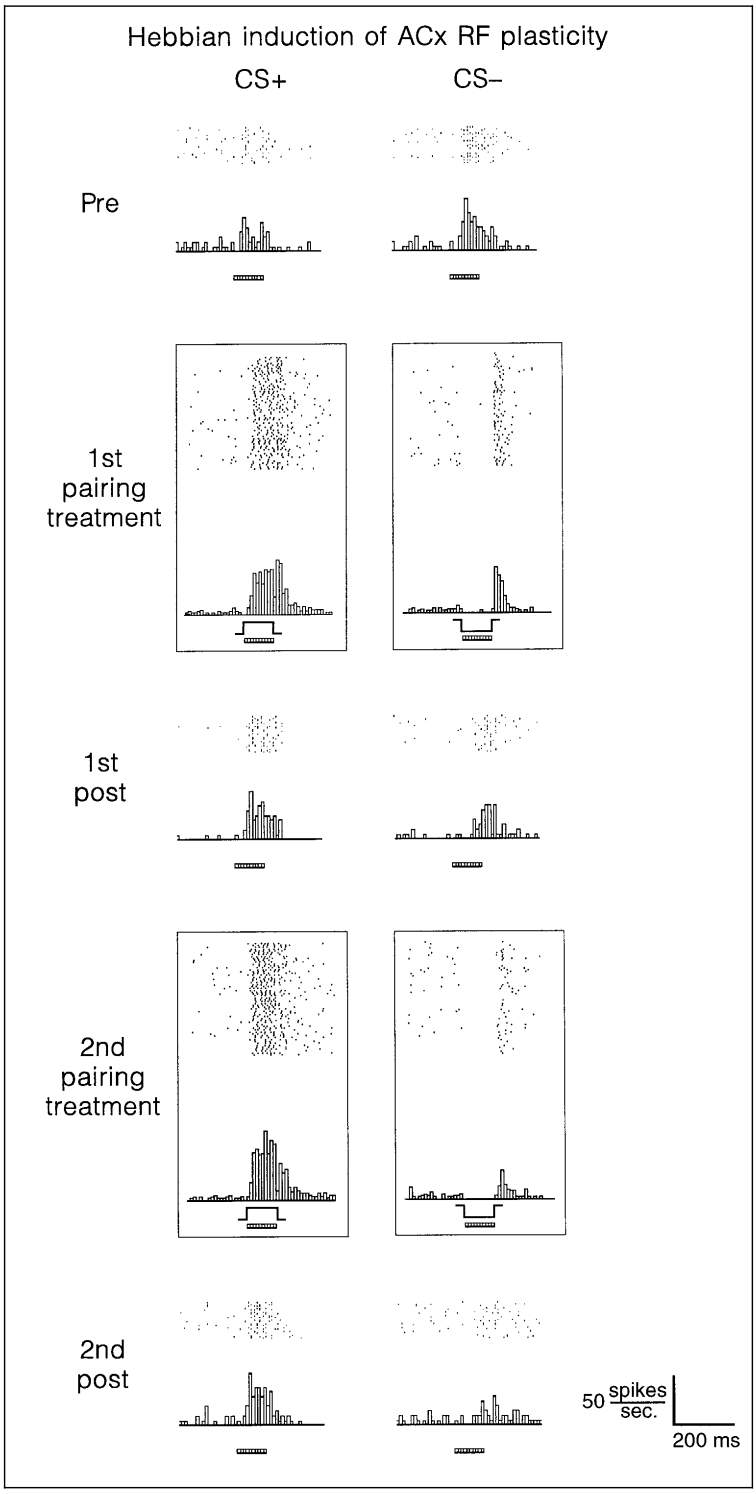

Fig. 8. Hebbian modification of cell responses. Tone-evoked histograms and rasters obtained prior to the first Hebbian pairing procedure (first row) indicate that the CS– (tone paired with negative, suppressive current, right column) evoked a greater response than the CS+ (tone paired with positive, excitatory current, left column). Pairing the CS+ with depolarizing current (second row, left column) resulted in a strong increase in cell responses, indicating that the current was effective in increasing the cell's excitability. In contrast, pairing the CS– with hyperpolarizing current (second right column) completely eliminated the tone-evoked response. Immediately following the first pairing procedure, there was a significant increase in the cell's response to the CS+ and a significant decrease in response to the CS– (third row, left and right columns, respectively.). A second pairing session with the same stimuli (fourth row) produced little change in response to the CS+ but a greater decrease in response to the CS– (fifth row) . Thus, induction of RF plasticity in the ACx follows Hebbian rules [figure adapted from Cruikshank and Weinberger, 1996a].

frequency map of animals that have been given behavioral training should contain increased representations of the trained frequency. This prediction was confirmed in the owl monkey given extensive behavioral training on an auditory discrimination task [Recanzone et al., 1993]. Frequency maps of trained animals contained significantly larger areas of cortex devoted to processing the trained frequency.

Résumé of Findings

Associative learning involves systematic changes in the frequency tuning of cells in the primary ACx of adult animals. Responses to a frequency of a behaviorally significant tone are facilitated relative to other frequencies, often resulting in shifts of tuning toward or to the significant frequency. This RF plasticity is highly specific, discriminative, rapidly induced, retained indefinitely, and is not an artifact of arousal or other state changes as it can be expressed under deep general anesthesia. All of these characteristics provide a basis for considering such RF plasticity to constitute 'physiological memory' as it satisfies the same criteria used to classify certain behavioral phenomena as representing 'behavioral associative memory'. We have formulated a cell-system-behavior model of RF plasticity based on the coordinated interaction of the lemniscal and nonlemniscal thalamocortical auditory systems with the NB cholinergic/muscarinic neuromodulatory system. We have hypothesized that these systems, interacting at the primary ACx via extended Hebbian rules, are sufficient for the induction and maintenance of RF plasticity. Several findings support this model, including the induction of associative RF plasticity by the pairing of a tone with activation of the NB. These studies of mechanism do not exclude other as yet uninvestigated systems, including noncholinergic modulators, complex intracortical processes and/or non-Hebbian actions, from either contributing to or themselves being sufficient for RF plasticity. This current progress report should be seen as constituting an initial line of inquiry rather than a definitive work.

Syntheses of Learning-Memory and Sensory Physiology

Adaptive behavior involves a continual interplay between an organism and its environment, both of which are dynamic. Sensory events provide an organism with information about both its environment and the effects of its own behavior on the environment. Thus, the mechanisms underlying the processing and storage of information about sensory events are at the foundation of the neural bases of adaptive behavior. Traditionally, the study of sensory events has been the domain of the sensory sciences, including psychophysics and sensory physiology, whereas the study of the acquisition and storage of information has been limited largely to the field of learning and memory. Historically, these fields have developed along separate, seldom intersecting, paths. But because they each concern the processing of information from the environment, some sorts of syntheses might benefit their common focus of inquiry. The present paper summarizes one such avenue of synthesis. It is perhaps only a historical curiosity that investigations of the systems neurophysiology of learning and memory have mainly used acoustic stimulation as a CS or other signal of impending positive or negative reinforcement and have, almost without exception, reported learning-induced changes in the ACx in response to such acoustic signal stimuli [reviewed in Weinberger and Diamond, 1987]. Such findings apparently had

little influence within either auditory physiology or the neurobiology of learning and memory. However, the approach and findings summarized in this paper may help bridge the gap because of the use of RFs to study learning. Since the construct of the RF is basic to sensory physiology, plasticity of RFs during learning can be examined within the broad framework of this field in general and can be related to prior fundamental findings, both from anesthetized subjects and from more recent studies of waking subjects. Indeed, it is noteworthy that many sensory physiology laboratories are now in the forefront of the study of experience-based adult sensory cortical plasticity, including both implicit and explicit studies of learning and memory [reviewed in Weinberger, 1995a]. Thus, it appears that much seminal research on neural mechanisms of adaptive behavior will take place within the enlarged domain of the sensory sciences. It is hoped that conceptual contributions, as well as behavioral methodologies, from the field of learning and memory will be incorporated into this exciting new line of research which has an uncertain but highly exciting future.

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