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Physiological Memory in Primary Auditory Cortex: Characteristics and Mechanisms

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"Physiological memory" is enduring neuronal change sufficiently specific to represent learned information. It transcends both sensory traces that are detailed but transient and long-term physiological plasticities that are insufficiently specific to actually represent cardinal details of an experience. The specificity of most physiological plasticities has not been comprehensively studied. We adopted receptive field analysis from sensory physiology to seek physiological memory in the primary auditory cortex of adult guinea pigs. Receptive fields for acoustic frequency were determined before and at various retention intervals after a learning experience, typified by single-tone delay classical conditioning, e.g., 30 trials of tone–shock pairing. Subjects rapidly (5–10 trials) acquire behavioral fear conditioned responses, indexing acquisition of an association between the conditioned and the unconditioned stimuli. Such stimulus–stimulus association produces receptive field plasticity in which responses to the conditioned stimulus frequency are increased in contrast to responses to other frequencies which are decreased, resulting in a shift of tuning toward or to the frequency of the conditioned stimulus. This receptive field plasticity is associative, highly specific, acquired within a few trials, and retained indefinitely (tested to 8 weeks). It thus meets criteria for "physiological memory." The acquired importance of the conditioned stimulus is thought to be represented by the increase in tuning to this stimulus during learning, both within cells and across the primary auditory cortex. Further, receptive field plasticity develops in several tasks, one-tone and two-tone discriminative classical and instrumental conditioning (habituation produces a frequency-specific decrease in the receptive field), suggesting it as a general process for representing the acquired meaning of a signal stimulus. We have proposed a two-stage model involving convergence of the conditioned and unconditioned stimuli in the magnocellular medial geniculate of the thalamus followed by activation of the nucleus basalis, which in turn releases acetylcholine that engages muscarinic receptors in the auditory cortex. This model is supported by several recent findings. For example, tone paired with NB stimulation induces associative, specific receptive field plasticity of at least a 24-h duration. We propose that physiological memory in auditory cortex is not "procedural" memory, i.e., is not tied to any behavioral conditioned response, but can be used flexibly.

Key Words: receptive field plasticity; primary auditory cortical plasticity; memory taxonomy; cholinergic/muscarinic mechanisms in cortical plasticity; nucleus basalis; representation of acquired stimulus importance.

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INTRODUCTION

The neocortex is widely believed to be a major site (perhaps the major site) of memory storage. It is likely to be a substrate for the long-term flexible use of information, in contrast, e.g., to the cerebellum which is involved in the learning of specific stimulus–response conditioned responses (CR, e.g., eyeblink). However, there has been much less research on the cortex than on structures such as the cerebellum, hippocampus, and amygdala. In particular, very little is known about how information is acquired, represented, and stored in the cortex.

This paper presents three sets of ideas:

1. Classical conditioning is *not* a type of "procedural" memory, because conditioning produces two types of memory: (a) sensory–motor [conditioned stimulus (CS)–CR], which is procedural and (b) sensory–sensory [CS–unconditioned stimulus (US)], which is not procedural.
2. Sensory–sensory associations involve the storage of specific information in the primary sensory cortex of the conditioned stimulus, based on shifts of receptive field tuning; the acquired behavioral importance of the CS in a CS–US association is *represented by the increased tuning to the CS*. While tuning shifts develop within individual cells, this effects an expansion of the cortex that is best tuned to the conditioned stimulus.
3. The cortical representation of learned significance in CS–US associations probably involves a two-stage process: (a) first, CS–US convergence and the induction of physiological plasticity in the thalamus and (b) second, long-term storage in the cortex requires activation of a neuromodulatory system, such as the basal forebrain cholinergic system, that is initiated from the thalamus.

Each point is considered in turn.

THE FIRST ASSOCIATIONS FORMED IN CLASSICAL CONDITIONING ARE SENSORY-SENSORY AND NONPROCEDURAL

Why Examine the Taxonomic Status of Classical Conditioning?

I first address the taxonomic status of sensory–sensory (CS–US) conditioning because I wish to establish the importance of this type of association as a sensory cortical process and thus as an entry point into determining how such memories are acquired and represented in the cortex. I will argue that classical conditioning is wrongly classified as a single type of memory, specifically procedural memory. Because procedural memory is viewed as a "noncognitive" form of memory, classical conditioning is disregarded as important for cortical memory. In the unfortunate exercise of a double standard, different questions and assumptions are attached to classical conditioning vs more cognitive tasks, such as remembering facts. Thus, for classical conditioning the major question asked is "How does the CS produce the conditioned response?" Such response-oriented biases do not arise for fact learning. This relegation of classical conditioning to stimulus–response learning wrongly disregards its actual breadth, which critically includes the acquisition of information about the causal fabric of the environment (Rescorla, 1988). My position is that S–S learning during classical conditioning involves the specific storage of information in the cortex

and that this information can be employed in a flexible manner in the future, rather than being tied to a specific behavioral conditioned response. Although space limitations preclude a full exposition of this issue, the general outlines of the problem can be set forth.

The Problem with Classical Conditioning as Procedural Learning

Taxonomies of memory that are based on the dichotomy between procedural and "declarative" memory classify "simple" (i.e., delay) classical conditioning as procedural memory (Squire, 1987; Squire & Zola, 1996). (Synonyms for procedural are "nondeclarative" and "implicit" but will be avoided to facilitate the discourse.) Classical conditioning is viewed as procedural because the formation of conditioned responses apparently does not involve conscious awareness in humans and does require a large number of training trials and because CRs seem to be motor skills (Squire, 1987).

However, classical conditioning procedures produce more than one form of learning. One of these, stimulus–response learning, perhaps best known at present by the eyeblink or nictitating membrane conditioned response (Thompson, in press), does seem to fit the procedural criteria. However, as long ago as the mid-1930s a distinction was made between such stimulus–response conditioned responses and a second type, stimulus–stimulus, that is more rapidly acquired and not restricted to a particular set of striated muscles (Schlosberg, 1937). This two-factor theory of classical conditioning has been maintained by subsequent workers; a particularly strong case was set forth by Konorski (1967).

More recently, a survey of the literature for delay aversive conditioning revealed a bimodal distribution in the rate of development of conditioned responses (Lennartz & Weinberger, 1992a). Rapidly developing CRs include associatively produced changes in blood pressure, galvanic skin response, heart rate, respiration, pupillary dilation, and conditioned suppression (an indirect measure of freezing). More slowly developing CRs are eyeblink, flexion, and nictitating membrane extension (Fig. 1). While it might be argued that differences in training protocols account for the bimodal distribution of learning rate, in fact the same difference is found within the same subject when both types of conditioned responses are monitored within the same training session. While Kehoe and Macrae (1994) have pointed out that the slowly acquired CRs can develop more rapidly with much longer intertrial intervals, these CRs still develop more slowly than heart rate, etc. (Lennartz & Weinberger, 1994).

A key difference between the CR types is that the rapidly developing CRs are nonspecific to the US while the slowly developing are "specific" types of CRs. Thus, blood pressure, galvanic skin response, heart rate, respiration, pupillary dilation, and conditioned suppression CRs all develop whether the US is shock to the eye or shock to the leg. In contrast, eyeblink and flexion CRs are specific to the locus of the noxious US. Nonspecific CRs apparently indicate that the subject has formed an association between the CS and the US, but has not yet produced a specific behavioral response that is targeted at the US. Later, a specific CR emerges as a response that is directed to the locus of the US and often precisely timed to occur immediately preceding the scheduled onset of the noxious US. The somatic muscular specificity is great. For example, there is no transfer between the shocked and the unshocked eye

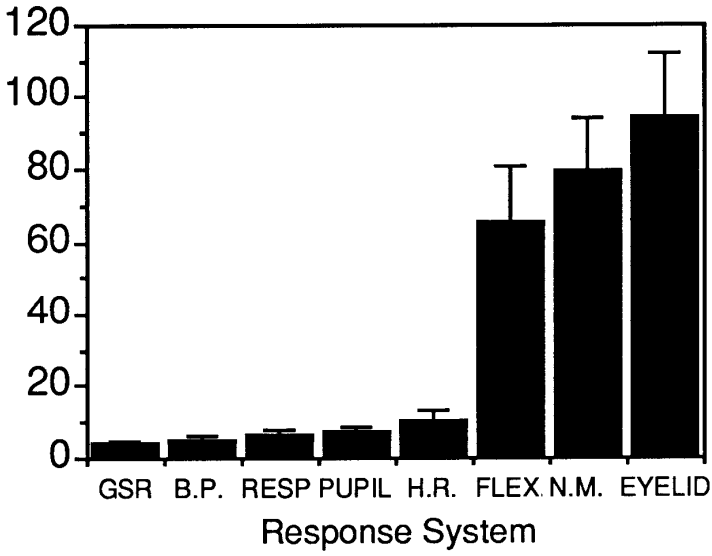


FIG. 1. Rates of development of conditioned responses for various effector systems in classical defensive conditioning. Data were compiled from an extensive review of the literature (Lennartz & Weinberger, 1992). Values are mean number of trials to the first reliable conditioned response (±SD). Note the bimodal distribution. Rapidly developing CRs are not specific to the locus of the noxious unconditioned stimulus; all develop in all defensive conditioning situations and reflect CS–US association and internal physiological conditioned adjustments. Slowly developing CRs are specific to the locus of the US; therefore only one of these develops in a given situation and reflects CS–CR association. B.P., blood pressure; FLEX, leg flexion; GSR, galvanic skin response; H.R., heart rate; N.M., nictitating membrane; PUPIL, pupillary dilation; RESP, respiration. (Reprinted with permission from R. C. Lennartz & N. M. Weinberger, 1992, *Psychobiology,* **20,** 93–119.)

for the nictitating membrane CR (e.g., reviewed in Thompson & Tracy, 1995). In contrast, S–S associations are more flexible behaviorally; for example, their expression is not limited to the circumstances or context of the original learning (e.g., LeDoux, Sakeguchi, & Reis, 1984). In short, nonspecific CRs index S–S (CS–US) association, whereas specific CRs index CS–CR (S–R) learning.

Returning to the taxonomy of memory, a recent distinction between "emotional responses" and "skeletal musculature" as two subsets of "simple classical conditioning" within the procedural category (Squire and Zola, 1996) does not go far enough, because it fails to recognize that the former indexes S–S association whereas the latter reflects S–R conditioning.

Where should S–S conditioning be placed if it is not procedural? In dichotomous taxonomies, there is only one alternative. But can S–S conditioning be comfortably accommodated within the "declarative memory" class? If one considers how S–S conditioning relates to training protocols used to study declarative memory, this might not be so far-fetched. Amnestics are impaired in paired associates learning, considered to index declarative memory (Reed & Squire, 1997; Squire, 1987). Also, cortical neural correlates of paired associates for geometric patterns in the monkey appear to depend upon an intact hippocampal system (Miyashita, in press). Given that each word or geometric pattern of a pair is a stimulus, paired associate learning closely resembles S–S association in classical conditioning, but with a new association for each pair of words or patterns. It would be interesting to determine whether cortical

plasticity involved with CS–US associations is impaired by hippocampal system lesions. In any event, CS–US associations may be a subclass of paired associate learning and thus accommodated within declarative memory.

However, there is also reason to exclude CS–US associations from declarative memory, at least with respect to those formed in delay conditioning (the subject of two-factor formulations as reviewed above). Clark and Squire (1998) recently found that normal subjects exhibit a positive relationship between amount of awareness of the tone–eye puff (CS–US) relationship and the level of eyeblink conditioning in trace (500 or 1250 ms) but not delay paradigms. Amnestics learned normally under delay conditions but not under trace conditions, presumably because with an impaired medial temporal system they lack the awareness of the S–S association. Interestingly, these results support the view that at least some CS–US learning is necessary for CS–CR learning that develops later in the same training circumstances. Regarding taxonomy, these findings strengthen the case for including trace CS–US conditioning as declarative but weaken the case for inclusion of delay S–S associations as declarative. If S–S delay association is excluded from both the declarative and the procedural categories, then it is left without a taxonomic home. This would suggest the need for reformulation or reconsideration of the current dichotomous taxonomy.

THE ACQUIRED IMPORTANCE OF A CONDITIONED STIMULUS IS STORED IN ITS PRIMARY SENSORY CORTEX CONSEQUENT TO ASSOCIATIVE RECEPTIVE FIELD PLASTICITY

Background: Why Use Receptive Field Analysis to Study Learning and Memory?

During the period of approximately 1950–1985 workers had firmly established that learning modifies responses in sensory cortex to stimuli that signal reward or punishment. Most extensively studied in the primary auditory cortex, it was shown for classical (and also instrumental) conditioning that responses to the conditioned stimulus change regardless of the type of recording (evoked potentials, multiple-unit recordings, single-unit discharges, or metabolic measures). This plasticity was shown to be associative rather than caused by sensitization, arousal, or other potentially nonlearning factors (reviewed in Weinberger & Diamond, 1987, 1988).

However, establishing any neurophysiological process as genuinely associative, be it sensory, cortical, hippocampal, or whatever, itself fails to adequately address the question of *how acquired information is represented*. There seem to be two major possibilities for all instances of associative physiological plasticity: they are either (a) sufficiently detailed to adequately represent specific acquired information or (b) they are not.

This issue cannot be resolved using a single conditioned stimulus because one stimulus value does not permit assessment of specificity. For example, if associative processes produce enhanced neural response to a CS, one cannot know whether such enhancement is specific to the CS itself or also extends to other stimuli. The use of a differential training paradigm can determine whether an association has been formed and also attacks the issue of degree of specificity. However, there are two problems which limit this approach. The first is that the use of only two values along a stimulus dimension provides

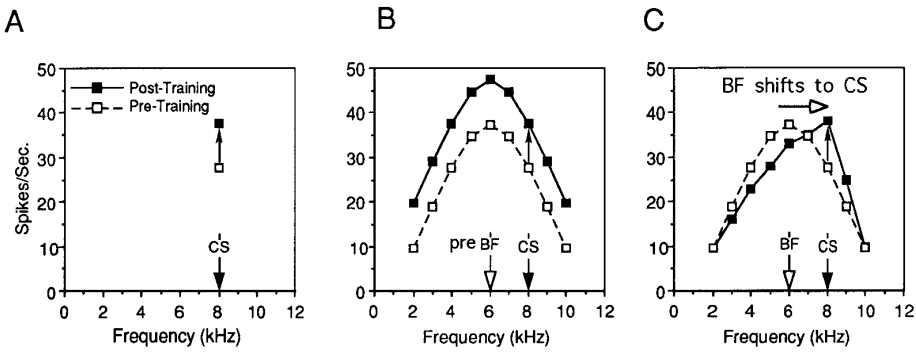


FIG. 2. Rationale for using receptive field analysis in learning and memory, illustrated for a hypothetical case in which an associative increase in response to an acoustic CS (8.0 kHz) developed after classical conditioning training (e.g., tone, shock). (A) Results from within-trial analysis illustrates the increased response, posttraining vs pretraining (upward arrow). The specificity of representation of information about acquired CS significance is unknown. (B and C) Acoustic frequency receptive fields obtained pre- and posttraining for the same amount of increased response to the CS frequency. (B) Posttraining RF shows equal response increase to all frequencies, yielding the conclusion that the increased response to the CS frequency did not represent specific information about this stimulus. (C) A shift in tuning is revealed, in which the CS frequency became the best frequency (peak of tuning curve), yielding the conclusion that conditioning produced a specific change in the representation of frequency information; i.e., CS acquired importance is represented by increased tuning to the CS frequency. (Reprinted from M. Gazzaniga (Ed.), *The Cognitive Neurosciences,* MIT Press, 1995.)

only the minimum amount of information about how the learning treatment has affected the processing of information.

The second, more critical, problem concerns the distinction between learning and performance (or "induction" and "expression" in the physiological plasticity literature). Regardless of whether a single stimulus or a differentiation paradigm is used, the effects of a learning treatment are assessed during training trials. However, acquisition data, useful as they are, are also subject to many confounding performance variables that are present during training trials, e.g., changes in motivation, tonic arousal. These could yield performance ("expression") that does not accurately reveal the true nature of modification of information representation. Hence, strong arguments have been made repeatedly against undue reliance on acquisition data (Mackintosh, 1985; Rescorla, 1988).

A solution to the problem is to combine paradigms from learning and sensory physiology. The latter provides the construct of the receptive field (RF), which involves determination of responses to an entire range of stimulus values. Thus, receptive fields can be determined for a cell before and at various times after any learning protocol. An additional benefit of this strategy is that the long-term retention of the plasticity can be assessed repeatedly in the same circumstances without involving other training, e.g., extinction when a CS is presented alone. The use of pretraining and postraining receptive fields to differentiate highly specific from less specific change of information processing is illustrated in Fig. 2.

Associative Receptive Field Plasticity in the Primary Auditory Cortex

The first RF study in primary sensory cortex revealed that classical conditioning produces a *highly specific* change in receptive fields (Bakin & Weinber-

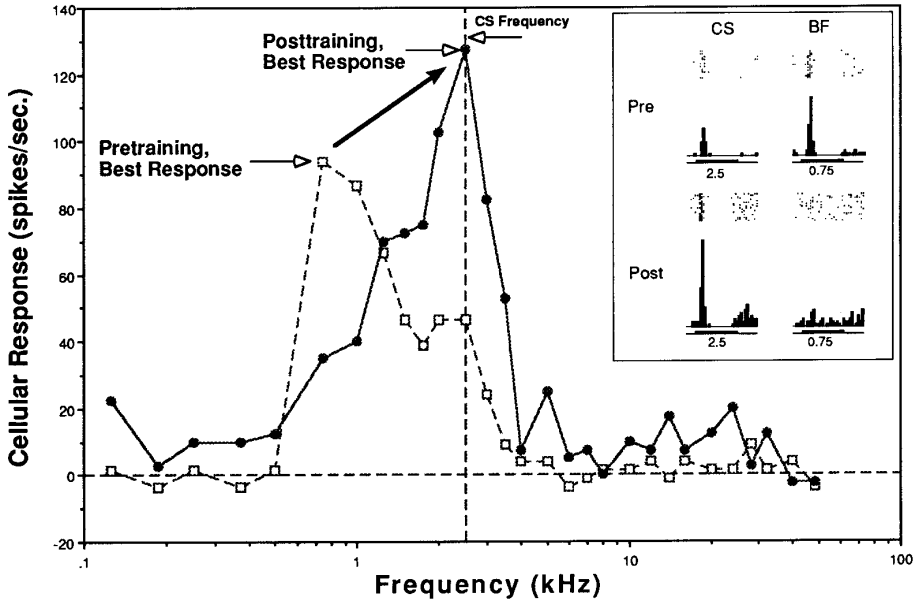
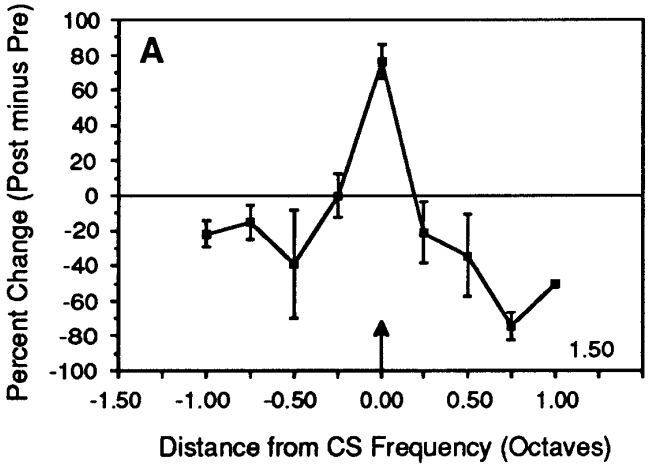
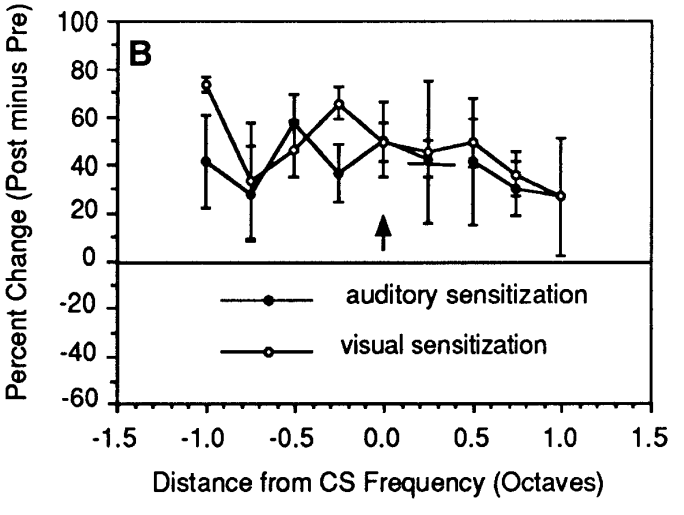


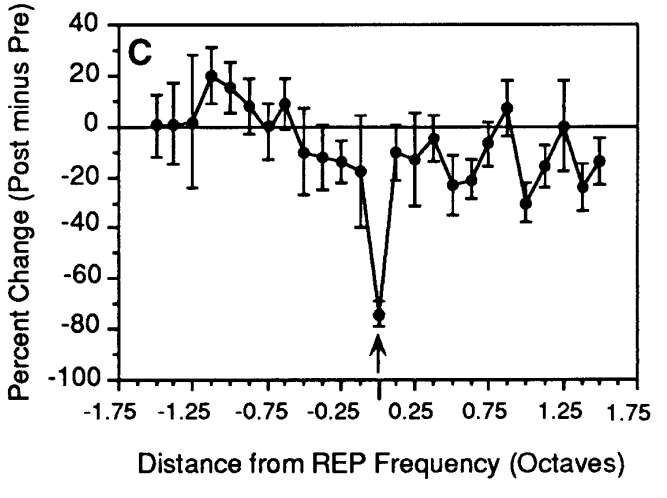
FIG. 3. An example of CS-specific receptive field plasticity for a single cell in the primary auditory cortex following classical conditioning. (Behavior and nonassociative controls not illustrated.) Pretraining, the best response (peak of tuning) was 0.75 kHz. After 30 trials of tone–shock pairing (CS was 2.5 kHz), the tuning had shifted to the CS frequency. Insets show poststimulus histograms and rasters (20 presentations of ascending frequency series to determine receptive field) for the CS and BF (pretraining peak of tuning) frequencies both before (pre) and after (post) training. Note in both histogram/rasters and tuning curves the increased response to the CS frequency and the decreased response to the pretraining best response. (N. M. Weinberger, R. Javid, & B. Lepan, 1993, *Proc. Natl. Acad. Sci. USA* **90,** 2394–2398. Copyright 1993 National Academy of Sciences, U.S.A.)

ger, 1990). Adult guinea pigs received 30 trials of a tone followed by a brief foot shock. Subjects rapidly (5–10 trials) acquired typical signs of conditioned fear. RFs immediately after training were changed to facilitate processing of the frequency of the CS. Responses to the CS frequency (and sometimes immediately adjacent frequencies) were increased, whereas responses to the pretraining best frequency (BF, peak of tuning curve) were usually reduced; responses to other non-CS frequencies were generally reduced or unchanged. The opposite signs of change were often large enough to shift frequency tuning toward or to the frequency of the conditioned stimulus (Fig. 3). This RF plastic-

FIG. 4. Specificity of RF plasticity for (A) conditioning, (B) sensitization, and (C) habituation, expressed as group normalized difference functions. These were computed for each subject by subtracting its pretraining RF from its posttraining RF, yielding individual difference functions. Because cells encountered across subjects have different tuning, direct averaging of difference curves would be inappropriate. Rather, each difference function was normalized to show change as a function of octave distance from the CS frequency (or habituated frequency) and averaged. Functions are mean group change (±SD). (A) Note conditioning produces increased response only at the CS frequency. (B) In contrast sensitization produces increases at all frequencies; this holds even when sensitization training consists of light and shock ("visual sensitization") instead of tone and shock, unpaired. (C) Note highly specific decrease at the frequency of the habituated stimulus. (From Edeline et al., 1993, *Behavioral Neuroscience* **107,** 539–557. Copyright©1993 American Psychological Association. Reprinted with permission.)


A
Percent Change (Post minus Pre)
100
80
60
40
20
0
-20
-40
-60
-80
-100
1.50
-1.50
-1.00
-0.50
0.00
0.50
1.00
Distance from CS Frequency (Octaves)


B
Percent Change (Post minus Pre)
100
80
60
40
20
0
-20
-40
-60
auditory sensitization
visual sensitization
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
Distance from CS Frequency (Octaves)


C
Percent Change (Post minus Pre)
40
20
0
-20
-40
-60
-80
-100
-1.75
-1.25
-0.75
-0.25
0.25
0.75
1.25
1.75
Distance from REP Frequency (Octaves)

ity is highly specific, with decreased responses to frequencies a fraction of an octave away (Fig. 4A). Further, RF plasticity is associative because it requires stimulus pairing (Bakin & Weinberger, 1990). Sensitization training produces only a general increase in response across the RF (Bakin, Lepan, & Weinberger, 1992) (Fig. 4B).

Several other characteristics make RF plasticity an attractive candidate for a process that subserves the acquisition, storage, and representation of behaviorally relevant information about the conditioned stimulus.

RF plasticity develops in other types of learning situations—two-tone classical discrimination training (Edeline, Neuenschwander-El Massioui, & Dutrieux, 1990a; Edeline & Weinberger, 1993) and both one-tone and two-tone discrimination instrumental avoidance training (Bakin, South, & Weinberger, 1996). It also develops during habituation (repeated presentation of a tone), but with the sign opposite to that of the CS+ during conditioning, i.e., a highly specific *decrease* to the repeated frequency (Condon & Weinberger, 1991; Fig. 4C). That RF plasticity develops in very different learning situations suggests it is a general process of information storage and representation.

RF plasticity develops very rapidly, in as few as five training trials, which is as soon as the appearance of the first behavioral signs of learning (Edeline, Pham, & Weinberger, 1993) (Fig. 5A). Therefore, RF plasticity is not limited to sensory/perceptual psychophysical learning which requires weeks of training (see Recanzone, Schreiner, & Merzenich, 1993).

RF plasticity lasts indefinitely; it is retained for extremely long periods of time, at least 2 months after training, as determined in cluster recordings (Weinberger, Javid, & Lepan, 1993; Fig. 5B). Of course, recordings over weeks cannot be shown to come from exactly the same neurons but the stability and specificity of the changes over weeks support an enduring learning effect at the recording sites. This documentation of months of long-term retention appears to be unique in the literature. Also, RF plasticity is extremely robust; while acquired in the waking state, it can be expressed with subjects under general anesthesia (Weinberger et al., 1993). This shows that neural S–S associations transcend the circumstances under which they were established (see previous section on memory taxonomies).

Associative Receptive Field Plasticity is Genuine

Two types of argument have suggested that RF plasticity is not genuine: first, that the recorded cell is lost but another cell tuned to a different frequency

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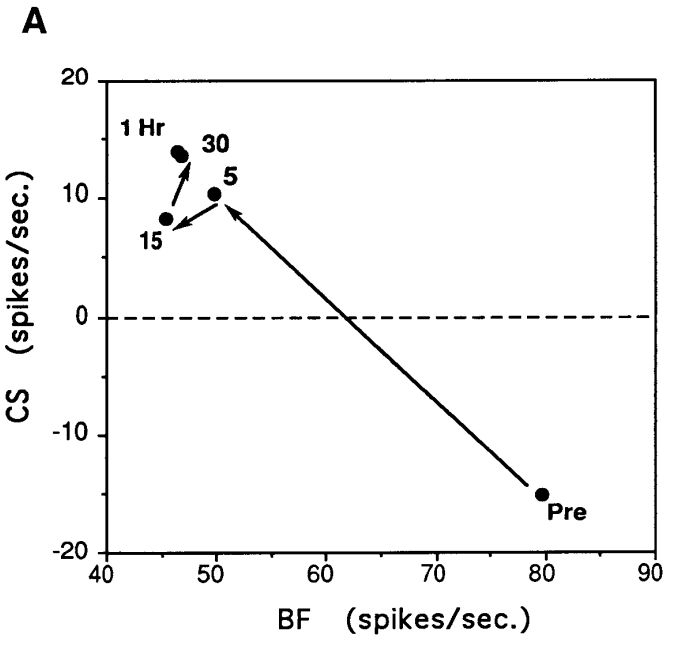
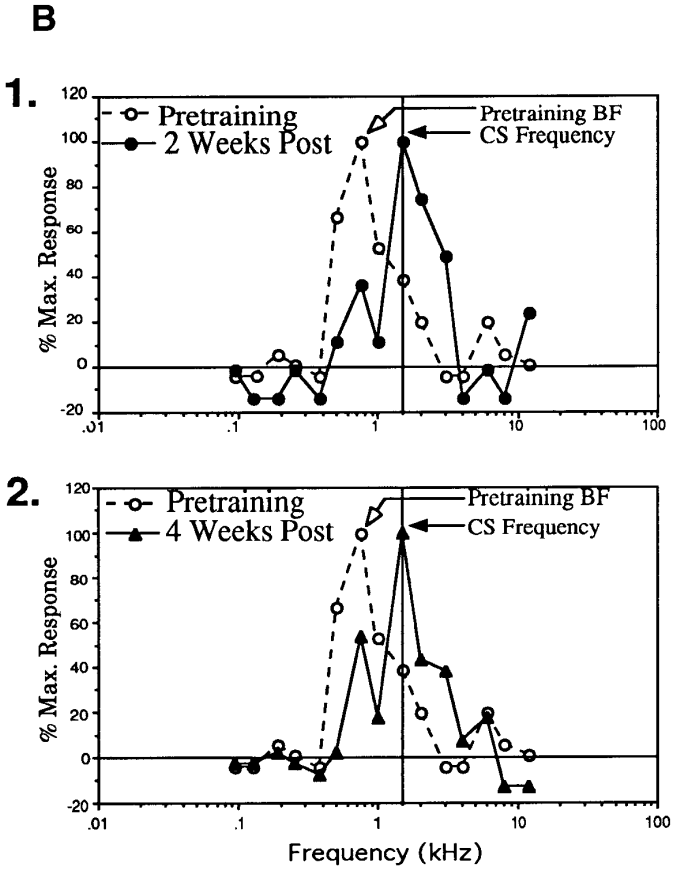
FIG. 5. Rapid development and very-long-term retention of receptive field plasticity. (A) Vector diagram shows an example of changes in response to CS and pretraining best frequency BF across an experiment in which RFs were determined before classical conditioning (Pre) and after 5, 15, and 30 trials of training and also 1 h after the 30th trial. Note in this case that at pretraining the best frequency was highly excitatory (~80 spikes/s) while the CS frequency was actually inhibitory (~minus 15 spikes/s). However, after only 5 trials of training, responses to the BF were greatly reduced whereas responses to the CS frequency became excitatory. There was little change thereafter, with the largest specific effects seen after the 30th trial and 1-h retention test. (B) Very-long-term retention of specific shift in tuning. Pretraining, the BF was 0.75 kHz and the CS was selected to be 1.5 kHz. Note the shift of tuning so that the CS frequency became the new BF, shown here (1) 2 and (2) 4 weeks posttraining, the last recording available for this subject. Training was performed in the waking guinea pig while all retention tests were conducted with the subjects under deep general anesthesia. (From Weinberger et al., 1993, *Proc. National Academy of Sciences* **90,** 2394–2398. Copyright 1993, National Academy of Sciences, U.S.A.)


A
1 Hr
30
5
15
Pre
CS (spikes/sec.)
BF (spikes/sec.)
20
10
0
-10
-20
40
50
60
70
80
90


B
1.
Pretraining
2 Weeks Post
Pretraining BF
CS Frequency
% Max. Response
2.
Pretraining
4 Weeks Post
Pretraining BF
CS Frequency
% Max. Response
Frequency (kHz)
.01
.1
1
10
100

takes its place, producing an apparent shift of tuning. Aside from continual control recordings of waveforms, there are other compelling reasons to reject this explanation. First, RF plasticity is associative. If learning-induced changes in tuning were artifacts of losing one cell but somehow then recording from another cell with the same waveform, then changes in tuning should also occur for sensitization protocols, but this does not occur. Second, shifts of tuning are overwhelmingly toward the CS, whereas shifts should be randomly directed if due to a change in the cell recorded. Third, changes are *opposite within the same cell* during discrimination training, i.e., increased response (and shift toward) the CS+ frequency, in contrast to decreased response to the CS− frequency (e.g., Fig. 6), but not the reverse.

Second, perhaps that presentation of the frequency of the CS during posttraining RF determination produces arousal which then causes increased response to the CS frequency. However, putative CS evoked arousal cannot occur in subjects under deep general anesthesia, yet RF plasticity is evident in this state (Lennartz & Weinberger, 1992b; Weinberger et al., 1993). Furthermore, the latency of cortical EEG arousal is longer (>150 ms; Weinberger & Lindsley, 1965) than that of evoked tuned discharges in the ACx (10–50 ms). Also, responses to tones delivered within a few hundred milliseconds after the CS frequency are unchanged or reduced, at the time when arousal would be present. Finally, direct physiological measures show no changes in arousal during receptive field determination (Bakin & Weinberger, 1990). This is probably related to the very different acoustic contexts during training trials (e.g., one frequency, ~5-s duration, rate ~1/1.5 min) vs RF determinations (e.g., 11 different frequencies, 100-ms duration, rate ~2/s) (see also Diamond & Weinberger, 1989).

Summary

In summary, frequency RFs in the primary auditory cortex of normal, adult animals are not fixed but are modified by learning. This plasticity is sufficient to change tuning to favor the processing of the conditioned stimulus. RF plasticity is associative, discriminative, and highly specific, develops very rapidly, can last indefinitely, and develops in both classical and instrumental conditioning; habituation produces a selective decrease in response to the repeated frequency. Moreover, although established in the waking state, RF plasticity

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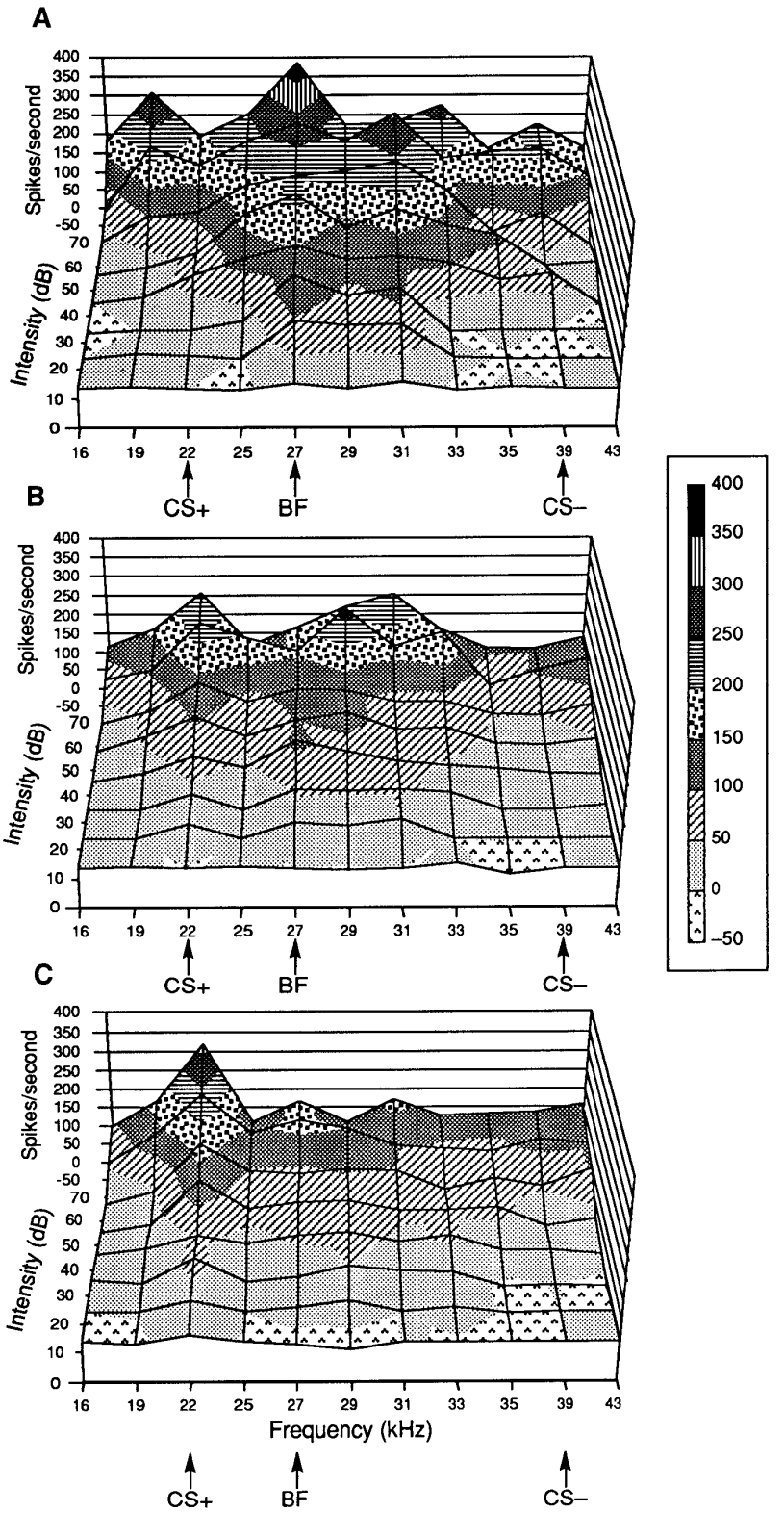
FIG. 6. CS-specific RF plasticity in discrimination training, across acoustic frequency and intensity. RFs across intensities are shown as a 3-D graph: *x*-axis shows frequency, y-axis shows response magnitude and the z-axis shows intensity (10-dB steps). (A) Pretraining, the BF was 27 kHz across intensities; the CS+ was selected to be at 22 kHz (in a "valley") while the CS− frequency was chosen to be at 39 kHz (a secondary "peak"). Discrimination training was then conducted (30 trials intermixed each of CS+ followed by shock and CS− without shock (70 dB), during which the guinea pig developed a discriminative cardiac conditioned response, indicating stimulus–stimulus association. (B) Immediately posttraining, tuning was changed to favor representation of the CS frequency. Increased excitatory responses developed at the CS+ frequency (22 kHz) and also at 31 and 33 kHz. In contrast, marked decreased responses were seen at the pretraining BF across intensity and also at the frequency of the CS−. (C) At the 1-h retention test (no additional training), the shift in tuning favoring the CS+ frequency was even more pronounced; the only peak of strong excitation was at the CS+ frequency and this was present across intensities. (Reprinted from Edeline and Weinberger, 1993, *Behavioral Neuroscience* **107,** 82–103. Copyright©1993 American Psychological Association. Reprinted with permission.)


A
B
C
Spikes/second
Intensity (dB)
400
350
300
250
200
150
100
50
0
-50
70
60
50
40
30
20
10
0
16
19
22
25
27
29
31
33
35
39
43
CS+
BF
CS–
Frequency (kHz)
400
350
300
250
200
150
100
50
0
–50

is sufficiently robust to be expressed in other states such as general anesthesia. Because learning retunes cells in the primary auditory cortex to favor the conditioned stimulus, its *acquired behavioral importance is represented by the increase in tuning* to this stimulus. The shifts in tuning within cells should produce an increased amount of cortex that is best tuned to the CS (Weinberger et al., 1990; see section below). Although the increased representation of a behaviorally important stimulus is established in a classical conditioning S–S paradigm, we believe this information can be employed by the animal across situation and time, in the service of adaptive behavior.

CORTICAL STORAGE OF STIMULUS IMPORTANCE MAY BE CAUSED BY TWO STAGES: CONVERGENCE IN THE THALAMUS AND ACTIVATION OF A CORTICAL NEUROMODULATORY SYSTEM

We formulated a preliminary two-stage model of the mechanisms underlying learning-induced receptive field plasticity several years ago (Weinberger, Ashe, Diamond, Metherate, McKenna, & Bakin, 1990). We briefly explain this model and present recent findings relevant to its utility and validity. Caveats and consideration of expansion of the model have been provided elsewhere (Weinberger, Ashe, & Edeline, 1994; Weinberger & Ashe, submitted for publication).

Stage 1: CS–US Convergence in the Magnocellular Medial Geniculate Nucleus

The first stage is thought to consist of the convergence of input from the CS and US within a nonlemniscal complex of the auditory thalamus, the magnocellular medial geniculate nucleus, and the closely associated posterior intralaminar nucleus (MGm/PIN). It has been established that tone and shock excite cells in the MGm (Love & Scott, 1969: Wepsic, 1966) and that cells within the MGm rapidly develop increased discharges to the CS due to associative processes (Birt & Olds, 1981; Edeline, Dutrieu, & Neuenschwander-El Massioui, 1988; Gabriel, Saltwick, & Miller, 1975; Ryugo & Weinberger, 1978; Weinberger, 1982). Receptive field analysis of the MGm in S–S conditioning (tone–shock) reveals the development and maintenance of highly specific plasticity, including shifts of tuning toward or to the frequency of the CS (Edeline, Neuenschwander-El Massioui, & Dutrieux, 1990b; Edeline & Weinberger, 1992; Lennartz & Weinberger, 1992b).

However, auditory cortical RF plasticity is not merely a passive reflection of RF plasticity projected from the MGm because its RFs are much more complex, multipeaked, and broadly tuned than are auditory cortical cells (Edeline & Weinberger, 1992; Lennartz & Weinberger, 1992b). Neither could enduring RF plasticity in the ACx simply be projected from the ventral medial geniculate nucleus (which does not respond to the US) because this lemniscal source of frequency-specific input to the ACx apparently develops limited transient RF plasticity which dissipates within an hour. This nucleus might participate in the induction of RF plasticity in the ACx, and this remains to be determined.

There is current uncertainty about the role of the lateral amygdala (AL), a topic which cannot be adequately considered here. Because the AL develops plasticity during tone–shock pairing (e.g., Maren, Porembra, & Gabriel, 1991) and receives multimodal input (reviewed in LeDoux, 1995), the role of the

MGm/PIN has been downplayed by some workers (Quirk, Armony, Repa, Li, & LeDoux, 1996), perhaps limited to providing CS input to the AL via its well-established projections to this nucleus (LeDoux, Farb, & Ruggerio, 1990). Although such a limited role for the MGm/PIN is consistent with the finding that lesions of this structure impair or block fear conditioning to an acoustic CS (LeDoux et al., 1984), the lesion findings are equally consistent with the projection of conditioned plasticity from the MGm/PIN to the AL. Moreover, this limited role for the MGm/PIN entails the curious, apparently impossible, position that neurons in the MGm/PIN that develop increased discharges to a tonal CS would have to project only their sensory attributes to the AL without also sending forth their increased discharges to the conditioned stimulus. Most likely MGm/PIN plasticity is "forwarded" to the AL, which itself is also a site at which plasticity forms. Resolution of this issue is not critical for the hypothesized second stage of subcortical involvement in auditory cortical RF plasticity.

Stage 2: Nucleus Basalis/Cholinergic Effects on Primary Auditory Cortex

We proposed that the MGm plasticity ultimately engages neurons in the cholinergic basal forebrain that project to the primary auditory cortex via the amygdala (MGm/PIN to lateral to central amygdala to nucleus basalis). Prior to studies of RF plasticity in learning, there was considerable evidence of nucleus basalis/cholinergic involvement in sensory cortical plasticity (reviewed in Dykes, 1997, and Weinberger, 1995) and in learning and memory (reviewed in Essman, 1983; McGaugh, 1989). Particularly relevant were reports that the nucleus basalis (NB) develops responses to conditioned stimuli (Richardson & Delong, 1986; Travis & Sparks, 1968; see also Whalen, Kapp, & Pascoe, 1994; Wilson & Rolls, 1990).

Resume of a Model of ACh Action in Learning Induced RF Plasticity

Based on these and other considerations, we hypothesized that during training trials the NB releases ACh in the cortex, which changes RFs by strengthening synapses activated by the CS frequency during training trials and weakening synapses for non-CS frequencies, thus producing a shift in tuning toward the CS. Briefly, the three subcortical systems that project to the ACx are thought to interact as follows. During CS–US pairing trials, the MGv provides unaltered, detailed frequency input to Layer IV of the auditory cortex. The MGm develops increased response to the CS. Its broad tuning and complex response properties provide little if any detailed frequency information to the auditory cortex. It projects its increased response to the CS to Layers I–II to the apical dendrites of pyramidal cells. The increased response to the CS in the MGm also activates the amygdala, which initiates autonomic and somatic behavioral conditioned responses and in turn activates the NB, thus producing an increased phasic release of ACh in the cortex.

The release of ACh amplifies the direct input from the MGm to the apical dendritic synapses by increasing membrane resistance and reducing after-hyperpolarization (AHP) (reviewed in Ashe & Weinberger, 1991). This would produce a widespread enhancement across the auditory cortex of postsynaptic activation during training trials. Via modified Hebbian rules (covariance), tone inputs to cortical pyramidal cells would be strengthened for the CS frequency

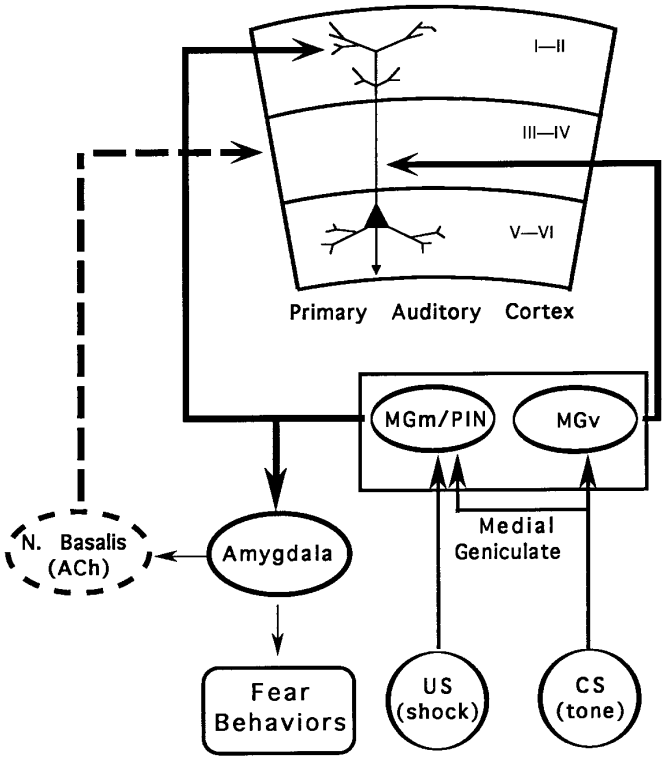


FIG. 7. Schematic showing the basic hypothesized architecture of a two-stage model of auditory cortical RF plasticity in learning. See text. MGm/PIN, magnocellular medial geniculate/posterior intralaminar complex; MGv, ventral medial geniculate nucleus. Roman numerals refer to cortical laminar zones.

because it is the only frequency active during CS presentation and because the CS input axons are active when postsynaptic cells are excited by the MGm and particularly by the NB cholinergic inputs. However, for synapses subserving non-CS frequencies, there is a discorrelation because *non-CS axons are inactive during training,* while the postsynaptic (pyramidal) cells are (as explained above) excited; this "mismatch" would produce a decrease in the strength of non-CS frequency synapses. The result is seen in posttraining cortical RFs as increased responses to the CS frequency and decreased responses to other frequencies. A summary of the model is provided in Fig. 7.

The feasibility of a Hebbian-type of mechanism in learning-induced receptive field plasticity is not obvious. As originally stated in the model, CS synapses were said to be facilitated and non-CS synapses were said to be weakened during training trials (because covariance occurred for the former but not for the latter). However, properly speaking, there are no CS and non-CS synapses, but only synapses that carry information for several acoustic frequencies. In the case of the primary auditory cortex, specific frequency information is provided by neurons of the ventral medial geniculate nucleus, each of which is "tuned" to a narrow band of frequencies, one of which is a particular best frequency, i.e., the peak of the tuning curve. Across the frequency spectrum, different neurons are tuned to different, but overlapping, frequency bands.

Following current understanding of neuronal function, if a given synapse is strengthened, then such strengthening applies to all 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 auditory cortex 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 & Ashe, submitted for publication). A prior sophistocated computational model also produces the same shifts of RF (Armony, Servan-Schreiber, Cohen, & LeDoux, 1995).

Naturally, Hebbian formulations have limitations and almost certainly do not account for every change in receptive field plasticity (for a critique see Edeline, 1996; for an analysis of the critique see Weinberger and Ashe, submitted for publication). For example, they may not account for a lack of change of response to frequencies distant from the CS that are outside of the RF, for which there would be a lack of presynaptic activation but cortical postsynaptic depolarization. Having recently reviewed both the logical requirements to substantiate Hebbian formulations and the current supportive evidence, we found fewer studies meeting critical criteria than might be supposed and have urged that undue emphasis not be placed on Hebbian rules, particularly to the exclusion of alternative approaches (Cruikshank & Weinberger, 1996a).

Recent Findings Generally Support the Model

Several, but not all, recent findings are consistent with the two-stage model. These will be reviewed briefly for the (a) auditory cortex, (b) medial geniculate and amygdala, and (c) nucleus basalis/cholinergic system. Most of these concern the basic two-stage architecture rather than intracortical synaptic actions. Interactions of glutamatergic and GABAergic transmitters in the ACx cannot be included here (for a review, see Weinberger & Ashe, submitted for publication).

Auditory Cortex

Expanded representation of CS frequency. The model explicitly predicted that conditioning should produce an enlargement of the representation of the CS frequency in primary auditory cortex because local shifts of tuning would alter the overall distribution of tuning, i.e., the frequency map (Weinberger et al., 1990). This has been since confirmed in a study of frequency discrimination training in the owl monkey (Recanzone et al., 1993).

Hebbian processes can change tuning. If Hebbian processes are at all sufficient for learning-induced RF plasticity, then responses to a tone presented during the time a postsynaptic cell is active should be increased while responses to a tone presented when a postsynaptic cell is inactive should be decreased. These hypotheses were tested by controlling the excitability of single postsynaptic (pyramidal) cells in the primary auditory cortex by application of paired juxtacellular excitatory or inhibitory current. Approximately one-third of neurons studied did exhibit changes in the predicted direction, with differential changes in response to tones that had been presented when the cells were either excited or inhibited (Fig. 8). Moreover, these effects could last for many minutes following pairing (Cruikshank & Weinberger, 1996b; see also Fregnac, Shulz, Thorpe, & Bienenstock, 1992; Shulz & Fregnac, 1992). No cells changed in the direction opposite of that predicted by the hypotheses.

Importantly, the state of activation of the auditory cortex proved to be important for the induction of plasticity. The pairing of tones and currents was significantly more effective when the EEG was not synchronized than when it was in high-voltage slow waves. As nucleus basalis stimulation shifts the EEG from a synchronized to a more activated state via cortical muscarinic receptors (Metherate & Ashe, 1994; Metherate, Cox, & Ashe, 1992), the increased induction of plasticity during a more activated state is consistent with the hypothesis that the NB/ACh system underlies RF plasticity.

Medial Geniculate and Amygdala

MGm plasticity precedes amygdala plasticity. The model predicts that learning-induced plasticity should be observed in the magnocellular medial geniculate nucleus at a shorter latency than in the amygdala. This has been reported during a two-tone discrimination paradigm in the rabbit in which single units were simultaneously recorded in the MGm and in the central nucleus of the amygdala (McEchron, McCabe, Gren, Llabre, & Schneiderman, 1995).

MGm heterosynaptic facilitation of acoustic responses in cortex. If the model is correct, then pairing an acoustic stimulus with electrical stimulation of the

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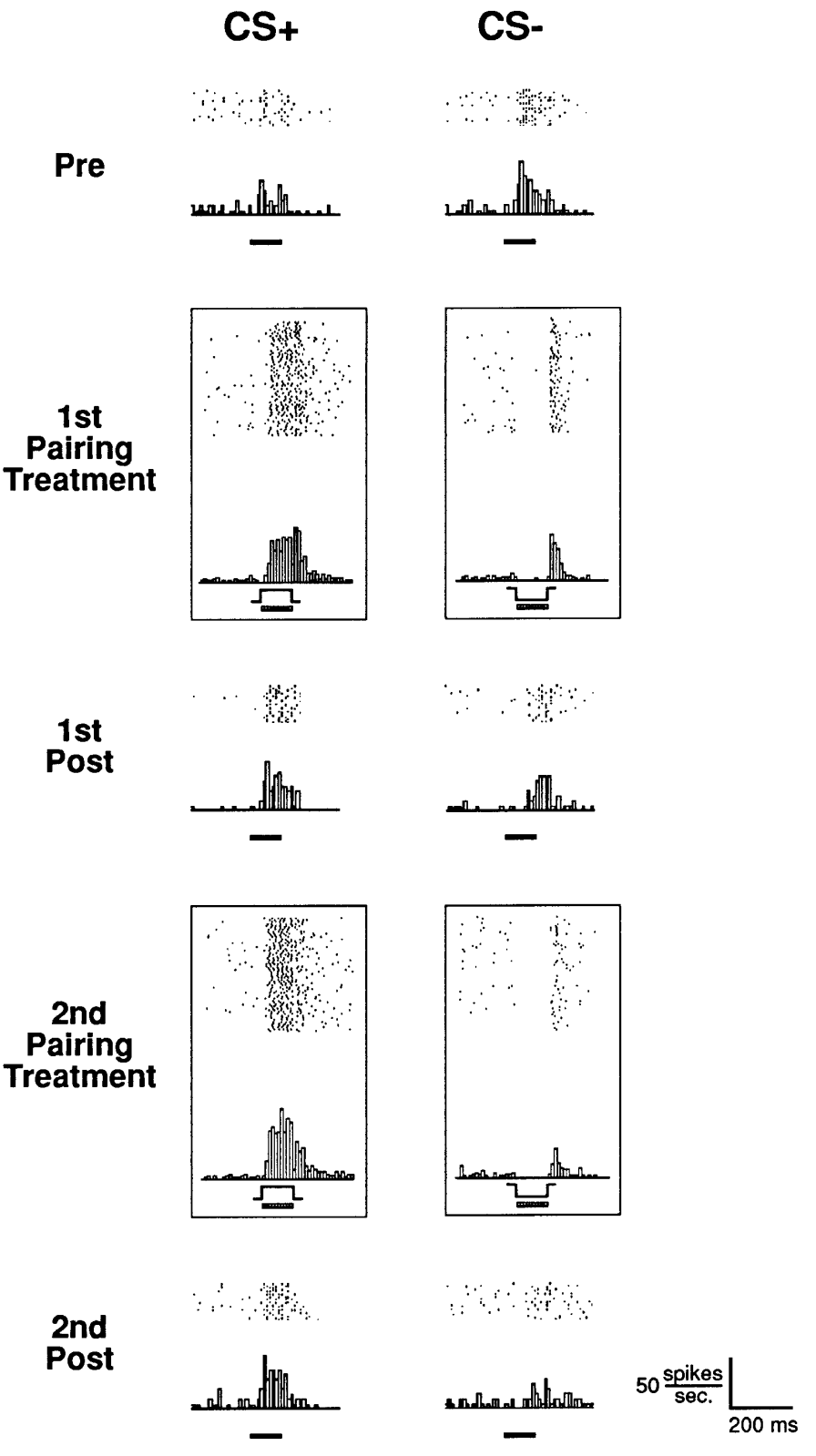
FIG. 8. "Hebbian" modification of a pyramidal cell's frequency responses. CS+ and CS− frequencies were selected to be on opposite sides of the peak of the tuning curve, with the CS+ being a weaker effective stimulus (Pre). The two tones were paired with juxtacellular current, CS+ with positive (excitatory) current, CS− with negative (suppressive) current; "1st pairing treatment" shows the effectiveness of the differential treatment. After pairing, responses to the CS+ increased whereas responses to the CS− decreased. A second pairing treatment in this case had little effect on the facilitation of responses to the CS+ but did produce further decreases, almost complete suppression of the response to the CS−. (Adapted from Cruikshank and Weinberger, 1996, *Journal of Neuroscience* **16,** 861–875. Reprinted with permission from The Society for Neuroscience.)


CS+
CS-
Pre
1st Pairing Treatment
1st Post
2nd Pairing Treatment
2nd Post
50 spikes/sec.
200 ms

MGm should produce long-lasting facilitation of evoked responses in the ACx. Such heterosynaptic facilitation has been found, with effects lasting for the 2-h duration of testing (Weinberger, Javid & Lepan, 1995).

Conditioning appears to produce synaptic plasticity in the MGm. Behavioral learning should produce synaptic plasticity, i.e., increased responses to acoustic input, in the MGm. McEchron, Green, Winters, Nolen, Schneiderman, and McCabe (1996) tested the efficacy of stimulation of the auditory input to the auditory thalamus (the brachium of the inferior colliculus, BIC) during tone–shock pairing in the rabbit. They reported long-lasting increased discharges of single neurons to BIC test stimuli (decreased latency, increased spike frequency), whereas responses to a nonauditory control input (superior colliculus) did not change. This is consistent with learning-induced synaptic plasticity in the MGM.

Amygdala lesions do not prevent cortical plasticity. The model includes the amygdala as the link between the MGm and the nucleus basalis. The MGm alone was hypothesized to have too weak a cortical influence to produce robust, long-term RF plasticity, because of its synapses on distal dendrites in Layer I, electronically far from the soma; NB-mediated release of ACh was hypothesized to amplify the MGm postsynaptic depolarization. Armony et al. (1998) have found that lesions of the amygdala do not prevent the development of increased short-latency discharges to the CS in the primary and other auditory fields in a tone-shock pairing paradigm. This finding is contrary to the model. Still unknown is whether the surviving cortical plasticity is associative and whether lesions prevented the activation of the NB and subsequent release of ACh into the cortex.

Nucleus Basalis/Cholinergic System

Facilitation of cortical acoustic responses by NB/cholinergic activation. The model assumes that direct activation of the NB should be able to facilitate responses to acoustic stimuli in the primary auditory cortex and that such facilitation should be mediated by ACh acting at muscarinic receptors in the auditory cortex. Indeed, stimulation of the nucleus basalis does produce long-lasting atropine-sensitive facilitation of evoked field potentials, cellular discharges, and EPSPs (Metherate & Ashe, 1991, 1993) elicited by stimulation of the medial geniculate and it facilitates neuronal discharges to tones (Edeline, Hars, Maho, & Hennevin, 1994; Edeline, Maho, Hars, & Hennevin, 1994; Hars, Maho, Edeline, & Hennevin, 1993). Pairing a tone with iontophoretic application of muscarinic agonists produces pairing-specific, atropine-sensitive modification of RFs that include shifts of tuning to or toward the frequency of the paired tone but also opposite effects that are not yet understood, which are inconsistent with the model (Metherate & Weinberger, 1990).

Associative plasticity in nucleus basalis precedes RF plasticity. If NB activation to a CS is causal to RF plasticity in the auditory cortex, then neurons in the NB should develop enhanced responses to the CS and should do so before cells in the auditory cortex exhibit learning-dependent effects. This has been found (Maho, Hars, Edeline, & Hennevin, 1995).

Associative induction of RF plasticity by nucleus basalis stimulation. The model implies that substituting stimulation of the NB for the peripheral shock

US should induce associative RF plasticity in the auditory cortex. Bakin and Weinberger (1996) found this result in urethane-anesthetized rats (Fig. 9). Such NB effects should also be very long-lasting. Bjordahl, Dimyan, and Weinberger (in press) obtained such NB-induced RF plasticity in waking guinea pigs, as tested up to 24 h after tone–NB pairing (Fig. 10). Such NB effects should be discriminative. This too has been found, in waking animals (Dimyan & Weinberger, submitted for publication). Finally tone paired with NB stimulation increases the representation for that tone in the cortical frequency map; this effect is said to be prevented by neurotoxic lesions of cholinergic NB cells (Kilgard and Merzenich, 1998).

OVERVIEW

The findings reviewed above lead to several conclusions, each of which will be elaborated very briefly.

Classical conditioning should not be classified as procedural learning. This training produces both stimulus–stimulus and stimulus–response associations. The former does not satisfy criteria for procedural memory. However, S–S associations may not satisfy criteria for declarative memory, despite the fact that they may be a subclass of paired associates learning. A reexamination of the procedural–declarative dichotomy is suggested. S–S associations in classical conditioning ought not to be ignored in attempts to understand the nature and mechanisms of information acquisition and storage in the cerebral cortex. Rather, they provide a novel avenue of investigation into the representation of acquired stimulus meaning (see below).

Initial associations in classical conditioning are sensory–sensory (CS–US) and involve the primary sensory cortex of the conditioned stimulus. CS–US associations are acquired very rapidly, in a few trials. They are indexed by nonspecific behavioral conditioned responses. During such learning, at least some information about this association is stored in the primary sensory cortex of the CS modality, best studied to date in the primary auditory cortex. This cortical plasticity is not necessarily linked to any particular behavioral conditioned response but is hypothesized to form a substrate of information that can be used flexibly, not restricted to the conditioning situation. This "cortical flexibility" hypothesis has not yet been investigated. This is likely to prove difficult but is nonetheless essential.

Specific information of the learned significance of the CS in an S–S association is stored in its primary auditory cortex by changes in synaptic weights for frequencies. This conclusion is based on shifts of tuning to favor CS frequencies and also by expanded representation of CS frequencies across the cortex. In principle, knowing the relative strength of representation of acoustic frequencies in primary auditory cortex would provide a "readout" of behavioral significance of frequency. The same principle may hold for other sensory systems and indeed for cortical representation of information in general. The "more tuning, more importance" relationship in learning seems to parallel the expanded representation within primary sensory cortex of sensory specializations in evolution. Examples include the call frequency in the echolocating mustached bat (Suga & Jen, 1976), the forepaw representation in the raccoon (Rasmusson, 1982), and the representation of the mystacial vibrissae in the rodent (Woolsey & Van der Loos, 1970). However, the learning-induced expan-

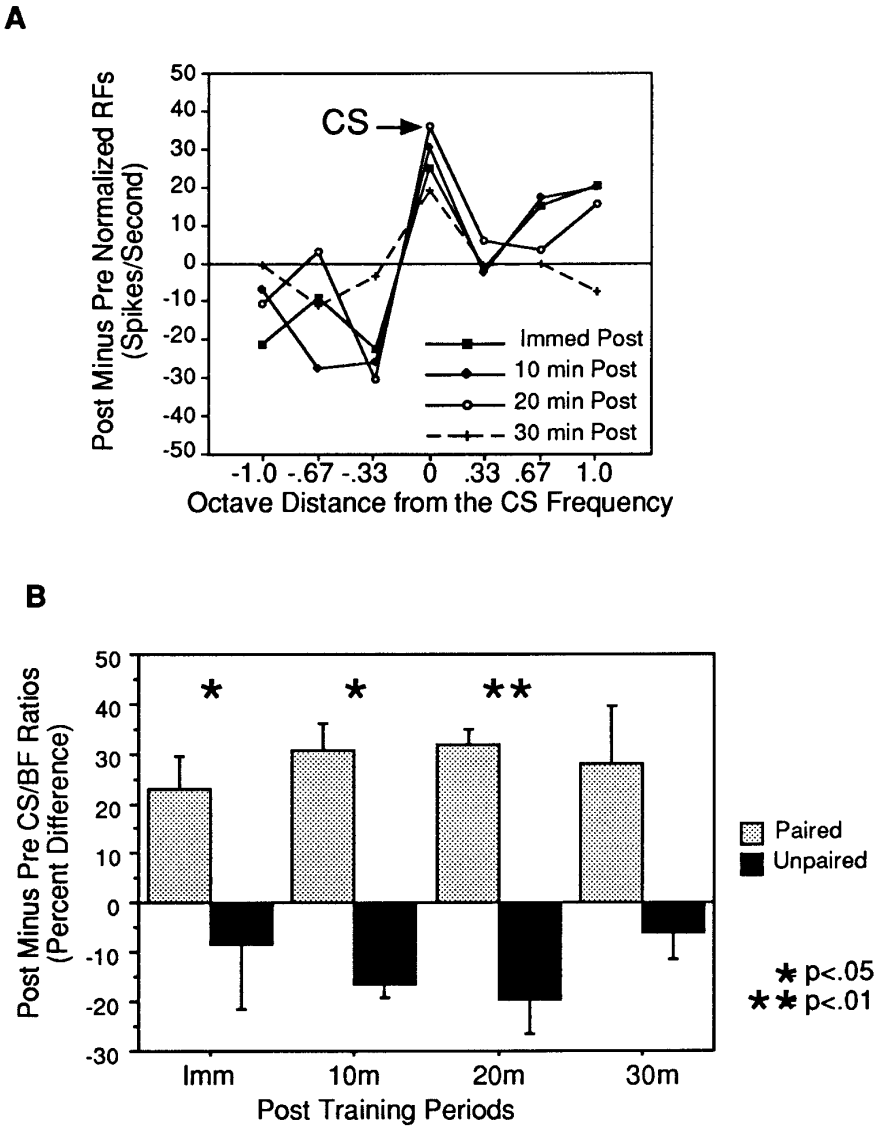


FIG. 9. Pairing a tone with stimulation of the nucleus basalis produces RF plasticity similar to that induced during behavioral conditioning (tone-shock pairing). (A) RF plasticity is specific and lasts many minutes in this acute experiment (subjects under urethane anesthesia). The difference between pairing and unpairing is given in normalized RF difference functions centered on the CS frequency (arrow). The average difference function for the unpaired group was subtracted from the average difference function for the paired group. This revealed that immediately after treatment paired CS/NB stimulation produced an increase in response that was limited to the CS frequency, with decreases or no change-within one-third of an octave of the CS frequency. This pattern of CS-specific RF modification due to pairing was retained for all postintervals tested, the effect being reduced at the 30-min retention period. (B) This RF plasticity is associative. Paired training produced a long-lasting increase at the frequency of the CS compared to the pretraining best frequency (BF) (mean ± SE). The CS/BF ratio increased approximately 20–30% at each period (immediate, 10, 20, 30 min) following paired CS/NB stimulation. In contrast, unpaired CS–NB presentation failed to produce an increase at any time period. The difference between paired and unpaired groups was statistically significant immediately and at 10 and 20 min posttreatment (reprinted from J. S. Bakin & N. M. Weinberger, 1996, *Proc. Natl. Acad. Sci. USA* **93,** 11219–11224. Copyright 1996 National Academy of Sciences, U.S.A.)

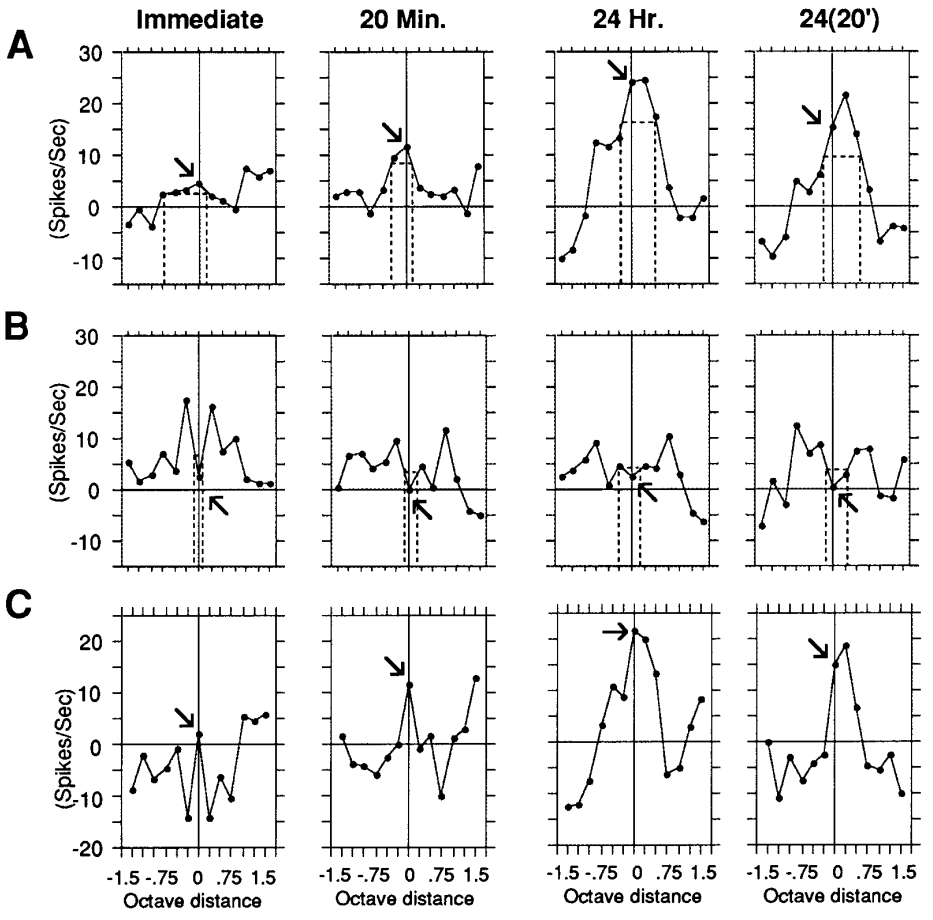


FIG. 10. NB stimulation in the waking guinea pig produces specific and very-long-lasting RF plasticity. Shown are normalized group receptive field difference functions [posttraining RFs minus pretraining RFs, centered on the CS frequency (arrow)] for several retention periods: immediately, 20 min, 1 day (24 Hr.) and 24 h plus 20 min (24(20′). (A) RF difference functions for the "Effective NB" group, i.e., for which a separate assay showed that NB stimulation produced EEG desynchronization in the auditory cortex. Note the absence of a strong effect immediately posttraining, the development of a CS-specific increase at 20 min, and the even stronger effects 24 h later. (B) RF difference functions for the "Non-Effective NB" group, for which NB stimulation proved unable to produce EEG desynchronization. Note the absence of CS-specific increased response; response change to the CS frequency tended to be at a local minimum. (C) The difference between the two groups (A minus B) reveals the overall differential effect and shows that the maximal increase in response was largely centered on the frequency of the CS. The dotted lines in A and B represent the 75% bandwidth markers. (Adapted from Bjordahl, Dimyan, and Weinberger, 1998, *Behavioral Neuroscience* **112,** 1–3. Copyright©1998 American Psychological Association. Reprinted with permission.)

sion that represents stimulus importance is more flexible, tracking changes in stimulus importance during life span. The receptive field plasticity now established for the primary auditory cortex may be a general mechanism, not limited to auditory or even to sensory cortices. That primary auditory cortex stores specific information about conditioned stimuli does not imply exclusivity; other regions of the brain undoubtedly store various aspects of information about signal stimuli.

Long-term memory in sensory cortex depends on a neuromodulatory system which itself contains no specific information about the experience. It should be noted that findings to date speak to "sufficiency" not "necessity." Thus, associative stimulation of the nucleus basalis is sufficient to induce specific RF plasticity in the auditory cortex but the effects of blockade of the NB cholinergic projections to the auditory cortex are not yet understood. Of course, other neuromodulatory systems (e.g., noradrenergic, serotonergic) engage the cortex. Although the model is based on the cholinergic system, other neuromodulators may be sufficient or necessary for the induction of receptive field plasticity or perhaps other aspects of plasticity that are substrates of cortical memory. The possibilities are many. The challenges are great.

REFERENCES

Armony, J. L., Servan-Schreiber, D., Cohen, J. D., & LeDoux, J. E. (1995). An anatomically constrained neural network model of fear conditioning. *Behavioral Neuroscience,* **109,** 246–257.

Armony, J. L., Quirk, G. J., & Le Doux, J. E. (1998). Differential effects of amygdala lesions on early and late plastic conditioning components of auditory cortex spike trains during fear conditioning. *Journal of Neuroscience,* **18,** 2592–2601.

Ashe, J. H., & Weinberger, N. M. (1991). Acetylcholine modulation of cellular excitability via muscarinic receptors: Functional plasticity in auditory cortex. *In* R. T. Richardson (Ed.), *Activation to acquisition: Functional aspects of the basal forebrain cholinergic system* (pp. 189–246). Boston: Birkhäuser.

Bakin, J. S., & Weinberger, N. M. (1990). Classical conditioning induces CS-specific receptive field plasticity in the auditory cortex of the guinea pig. *Brain Research,* **536,** 271–286.

Bakin, J. S., & Weinberger, N. M. (1996). Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proceedings of the National Academy of Sciences of the USA,* **93,** 11219–11224.

Bakin, J. S., Lepan, B., & Weinberger, N. M. (1992). Sensitization induced receptive field plasticity in the auditory cortex is independent of CS-modality. *Brain Research,* **577,** 226–235.

Bakin, J. S., South, D. A., & Weinberger, N. M. (1996). Induction of receptive field plasticity in the auditory cortex of the guinea pig during instrumental avoidance conditioning. *Behavioral Neuroscience,* **110,** 905–913.

Birt, D., & Olds, M. (1981). Associative response changes in lateral midbrain tegmentum and medial geniculate during differential appetitive conditioning. *Journal of Neurophysiology,* **46,** 1039–1055.

Bjordahl, T. S., Dimyan, M. A., & Weinberger, N. M. (1998). Induction of long term receptive field plasticity in the auditory cortex of the waking guinea pig by stimulation of the nucleus basalis. *Behavioral Neuroscience,* **112,** 1–3.

Clark, R. E., & Squire, L. R. (1998). Classical conditioning and brain systems: The role of awareness. *Science,* **280,** 77–81.

Condon, C. D., & Weinberger, N. M. (1991). Habituation produces frequency-specific plasticity of receptive fields in the auditory cortex. *Behavioral Neuroscience,* **105,** 416–430.

Cruikshank, S. J., & Weinberger, N. M. (1996a). Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: A critical review. *Brain Research Reviews,* **3,** 191–228.

Cruikshank, S. J., & Weinberger, N. M. (1996b). Receptive-field plasticity in the adult auditory cortex induced by Hebbian covariance. *Journal of Neuroscience,* **16,** 861–875.

Diamond, D. M., & Weinberger, N. M. (1989). The role of context in the expression of learning-induced plasticity of single neurons in auditory cortex. *Behavioral Neuroscience,* **103,** 471–494.

Dimyan, M. A., & Weinberger, N. M. Discriminative receptive field plasticity induced in the auditory cortex by stimulation of the basal forebrain. Submitted for publication.

Dykes, R. W. (1997). Mechanisms controlling neuronal plasticity in somatosensory cortex. *Canadian Journal of Physiological Pharmacology,* **75,** 535–545.

Edeline, J-M. (1996). Does Hebbian synaptic plasticity explain learning-induced sensory plasticity in adult mammals? *Journal de Physiologie,* **90,** 271–276.

Edeline, J-M., & Weinberger, N. M. (1992). Associative retuning in the thalamic source of input to the amygdala and auditory cortex: Receptive field plasticity in the medial division of the medial geniculate body. *Behavioral Neuroscience,* **106,** 81–105.

Edeline, J. M., & Weinberger, N. M. (1993). Receptive field plasticity in the auditory cortex during frequency discrimination training: Selective retuning independent of task difficulty. *Behavioral Neuroscience,* **107,** 82–103.

Edeline, J.-M., Dutrieux, G., & Neuenschwander-El Massioui, N. (1988). Multiunit changes in hippocampus and medial geniculate body in free-behaving rats during acquisition and retention of a conditioned response to a tone. *Behavioral Neural Biology,* **50,** 61–79.

Edeline, J-M., Hars, B., Maho, C., & Hennevin, E. (1994). Transient and prolonged facilitation of tone-evoked responses induced by basal forebrain stimulations in the rat auditory cortex. *Experimental Brain Research,* **97,** 373–386.

Edeline, J-M., Maho, C., Hars, B., & Hennevin, E. (1994). Non-awaking basal forebrain stimulation enhances auditory cortex responsiveness during slow-wave sleep. *Brain Research,* **636,** 333–337.

Edeline, J-M., Neuenschwander-El Massioui, N., & Dutrieux, G. (1990a). Frequency-specific cellular changes in the auditory system during acquisition and reversal of discriminative conditioning. *Psychobiology,* **18,** 382–393.

Edeline, J-M., Neuenschwander-el Massioui, N., & Dutrieux, G. (1990b). Discriminative long-term retention of rapidly induced multiunit changes in the hippocampus, medial geniculate and auditory cortex. *Behavioral Brain Research,* **39,** 145–155.

Edeline, J-M., Pham, P., & Weinberger, N. M. (1993). Rapid development of learning-induced receptive field plasticity in the auditory cortex. *Behavioral Neuroscience,* **107,** 539–557.

Essman, W. B. (1983). *Clinical pharmacology of learning and memory* (pp. 15–42). New York: S.P. Medical.

Fregnac, Y., Shulz, D., Thorpe, E., & Bienenstock, E. (1992). Cellular analogs of visual cortical epigenesis. I. Plasticity of orientation selectivity. *Journal of Neuroscience,* **12,** 1280–1300.

Gabriel, M., Saltwick, S. E., & Miller, J. D. (1975). Conditioning and reversal of short-latency multiple-unit responses in the rabbit medial geniculate nucleus. *Science,* **189,** 1108–1109.

Hars, B., Maho, C., Edeline, J. M., & Hennevin, E. (1993). Basal forebrain stimulation facilitates tone-evoked responses in the auditory cortex of awake rat. *Neuroscience,* **56,** 61–74.

Kehoe, E. J., & Macrae, M. (1994). Classical conditioning of the rabbit nictitating membrane response can be fast or slow: Implications for Lennartz and Weinberger's (1992) two-factor theory. *Psychobiology,* **22,** 1–4.

Kilgard, M. P., & Merzenich, M. M. (1990). Cortical map reorganization enabled by nucleus basalis activity. *Science,* **279,** 1714–1718.

Konorski, J. (1967). *Integrative activity of the brain: An interdisciplinary approach*. Chicago: Univ. of Chicago Press.

LeDoux, J. E. (1995). Emotion: Clues from the brain. *Annual Review of Psychology,* **46,** 2009–2035.

LeDoux, J. E., Farb, C. F., & Ruggiero, D. D. (1990). Topographic organization of neurons in the acoustic thalamus that project to the amygdala. *Journal of Neuroscience,* **10,** 1043–1054.

LeDoux, J. E., Sakaguchi, A., & Reis, D. J. (1984). Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned by acoustic stimuli. *Journal of Neuroscience,* **4,** 683–698.

Lennartz, R. C., & Weinberger, N. M. (1992a). Analysis of response systems in Pavlovian conditioning reveals rapidly vs slowly acquired conditioned responses: Support for two-factors, implications for behavior and neurobiology. *Psychobiology,* **20,** 93–119.

Lennartz, R. C., & Weinberger, N. M. (1992b). Frequency-specific receptive field plasticity in the medial geniculate body induced by Pavlovian fear conditioning is expressed in the anesthetized brain. *Behavioral Neuroscience,* **106,** 484–497.

Lennartz, R. C., & Weinberger, N. M. (1994). A comparison of nonspecific and nictitation membrane conditioned responses: Additional support for two-factor theories. *Psychobiology,* **22,** 5–15.

Love, J. A., & Scott, J. W. (1969). Some response characteristics of cells of the magnocellular division of the medial geniculate body of the cat. *Canadian Journal of Physiological Pharmacology,* **47,** 881–888.

Mackintosh, N. J. (1985). Varieties of conditioning. *In* N. M. Weinberger, J. L. McGaugh, & G. Lynch (Eds.), *Memory systems of the brain* (pp. 335–351). New York: Guilford Press.

Maho, C., Hars, B., Edeline, J-M., & Hennevin, E. (1995). Conditioned changes in the basal forebrain: Relations with learning-induced cortical plasticity. *Psychobiology,* **23,** 10–25.

Maren, S., Porembra, A., & Gabriel, M. (1991). Basolateral amygdaloid multi-unit neuronal correlates of discriminative avoidance learning in rabbits. *Brain Research,* **549,** 311–316.

McEchron, M. D., McCabe, P. M., Green, E. J., Llabre, M. M., & Schneiderman, N. (1995). Simultaneous single unit recording in the medial nucleus of the medial geniculate and amygdaloid central nucleus throughout habituation, acquisition, and extinction of the rabbit's classically conditioned heart rate. *Brain Research,* **682,** 157–166.

McEchron, M. D., Green, E. J., Winters, R. W., Nolen, T. G., Schneiderman, N., & McCabe, P. M. (1996). Changes of synaptic efficacy in the medial geniculate nucleus as a result of auditory classical conditioning. *Journal of Neuroscience,* **16,** 1273–1283.

McGaugh, J. L. (1989). Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. *Annual Review of Neuroscience,* **12,** 255–287.

Metherate, R., & Ashe, J. H. (1991). Basal forebrain stimulation modifies auditory cortex responsiveness by an action at muscarinic receptors. *Brain Research,* **559,** 163–167.

Metherate, R., & Ashe, J. H. (1993). Nucleus basalis stimulation facilitates thalamocortical synaptic transmission in rat auditory cortex. *Synapse,* **14,** 132–143.

Metherate, R., & Ashe, J. H. (1994). Ionic flux contributions to neocortical slow waves and nucleus basalis-mediated activation: Whole-cell recordings *in vivo. Journal of Neuroscience,* **13,** 5312–5323.

Metherate, R., Cox, C. L., & Ashe, J. H. (1992). Cellular bases of neocortical activation: Modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. *Journal of Neuroscience,* **12,** 4701–4711.

Metherate, R., & Weinberger, N. M. (1990). Cholinergic modulation of responses to single tones produces tone-specific receptive field alterations in cat auditory cortex. *Synapse,* **6,** 133–145.

Miyashita, Y., Kameyama, M., Hasegawa, I., & Fukushima, T. (1998). Consolidation of visual associative long-term memory in the temporal cortex of primates. *Neurobiology of Learning and Memory,* in press.

Quirk, G. L., Armony, J. L., Repa, J. C., Li, X.-F., & LeDoux, J. E. (1996). Emotional memory: A Search for sites of plasticity. *In Cold Spring Harbor symposia on quantitative biology* (Volume LXI, pp. 247–257). New York: Cold Spring Harbor Laboratory Press.

Rasmusson, D. D. (1982). Reorganization of raccoon somatosensory cortex following removal of the fifth digit. *Journal of Comparative Neurology,* **205,** 313–326.

Recanzone, G. H., Schreiner, C. E., & Merzenich, M. M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *Journal of Neuroscience,* **13,** 87–103.

Reed, J. M., & Squire, L. R. (1997). Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behavioral Neuroscience,* **111,** 667–675.

Rescorla, R. A. (1988). Behavioral studies of Pavlovian conditioning. *Annual Review of Neuroscience,* **11,** 329–352.

Richardson, R. T., & DeLong, M. R. (1986). Nucleus basalis of Meynert neuronal activity during a delayed response task in monkey. *Brain Research,* **399,** 364–368.

Ryugo, D. K., & Weinberger, N. M. (1978). Differential plasticity of morphologically distinct neuron populations in the medial geniculate body of the cat during classical conditioning. *Behavioral Biology,* **22,** 275–301.

Schlosberg, H. (1937). The relationship between success and the laws of conditioning. *Psychological Review,* **44,** 379–394.

Shulz, D., & Fregnac, Y. (1992). Cellular analogs of visual cortical epigenesis. II. Plasticity of binocular integration. *Journal of Neuroscience,* **12,** 1301–1318.

Squire, L. (1987). *Memory and brain.* New York: Oxford Univ. Press.

Squire, L. R., & Zola, S. M. (1996). Memory impairment and the medial temporal lobe. *In Cold Spring Harbor symposia on quantitative biology* (Vol. LXI, pp. 185–196). New York: Cold Spring Harbor Laboratory Press.

Suga, N., & Jen, P. H-S. (1976). Disproportionate tonotopic representation for processing CF-FM sonar signals in the mustache bat auditory cortex. *Science,* **194,** 542–544.

Thompson, R. F., Thompson, J. K., Kim, J. K., Krupa, D. J., & Shinkman, P. G. (1998). The nature of reinforcement in cerebellar learning. *Neurobiology of Learning and Memory,* in press.

Thompson, R. F., & Tracy, J. A. (1995). Cerebellar localization of a memory trace. *In* J. L. McGaugh, F. Bermudez-Rattoni, & R. A. Prado-Alcala (Eds.), *Plasticity in the central nervous system: Learning and memory* (pp. 107–127). Mahwah, NJ: Erlbaum.

Travis, R. P., & Sparks, D. L. (1968). Unitary responses and discrimination learning in the squirrel monkey: The globus pallidus. *Physiology and Behavior,* **3,** 187–196.

Weinberger, N. M., & Lindsley, D. B. (1964). Behavioral and electroencephalographic arousal to contrasting novel stimulation. *Science,* **144,** 1355–1357.

Weinberger, N. M. (1982). Sensory plasticity and learning: The magnocellular medial geniculate nucleus of the auditory system. *In* C. D. Woody (Ed.), *Conditioning: Representation of involved neural function* (pp. 697–710). New York: Plenum.

Weinberger, N. M., & Diamond, D. M. (1987). Physiological plasticity of single neurons in auditory cortex: Rapid induction by learning. *Progress in Neurobiology,* **29,** 1–55.

Weinberger, N. M., & Diamond, D. M. (1988). Dynamic modulation of the auditory system by associative learning. *In* G. M. Edelman, W. E. Gall, & W. M. Cowan (Eds.), *Auditory Function: The Neurobiological Bases of Behavior* (pp. 485–512). New York: Wiley.

Weinberger, N. M., Javid, R., & Lepan, B. (1993). Long-term retention of learning-induced receptive-field plasticity in the auditory cortex. *Proceedings of the National Academy of Sciences of the USA* **90,** 2394–2398.

Weinberger, N. M., Javid, R., & Lepan, B. (1995). Heterosynaptic long-term facilitation of sensory evoked responses in the auditory cortex by stimulation of the magnocellular medial geniculate body. *Behavioral Neuroscience,* **109,** 10–17.

Weinberger, N. M., Ashe, J. H., Diamond, D. M., Metherate, R., McKenna, T. M., & Bakin, J. (1990). Retuning auditory cortex by learning: A preliminary model of receptive field plasticity. *Concepts in Neuroscience,* **1,** 91–132.

Weinberger, N. M., Ashe, J. H., & Edeline, J.-M. (1994). Learning-induced receptive field plasticity in the auditory cortex: Specificity of information storage. *In* J. Delacour (Ed.), *The memory system of the brain* (pp. 590–635). Singapore: World Scientific.

Weinberger, N. M. (1995). Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Annual Review of Neuroscience,* **18,** 129–158.

Weinberger, N. M. (1995). Retuning the brain by fear conditioning. *In* M. Gazzaniga (Ed.), *The Cognitive Neurosciences,* pp. 1071–1089. Cambridge, MA: MIT Press.

Weinberger, N. M., & Ashe, J. A. (submitted). A model of learning-induced physiological memory in the cerebral cortex: Evaluation and prospects. Submitted for publication.

Wepsic, J. G. (1966). Multimodal sensory activation of cells in the magnocellular medial geniculate nucleus. *Experimental Neurology,* **15,** 299–318.

Whalen, P. J., Kapp, B. S., & Pascoe, J. P. (1994). Neuronal activity within the nucleus basalis and conditioned neocortical electroencephalographic activation. *Journal of Neuroscience,* **14,** 1623–1633.

Wilson, F. A. W., & Rolls, E. T. (1990). Learning and memory is reflected in the responses of reinforcement-related in the primate basal forebrain. *Journal of Neuroscience,* **10,** 1254–1267.

Woolsey, T. A., & Van der Loos, H. (1970). The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitechtonic units. *Brain Research,* **17,** 205–242.